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REVIEW ARTICLE

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Diagnosis and treatment of community-acquired pneumonia in adults: 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association

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Abbreviations: ATS, American Thoracic Society; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; BCYE, buffered charcoal-yeast extract; BUN, blood urea nitrogen; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; CAP, community-acquired pneumonia; CARTIPS, Community-Acquired Respiratory Tract Infection Pathogen Surveillance; CF, complement fixation test; CFDA, China Food and Drug Administration; CMA, Chinese Medical Association; CRP, C-reactive protein; CTS, Chinese Thoracic Society; DFA, direct fluorescent antibody test; DT, Sabin-Feldman dye test; ECMO, extracorporeal membrane oxygenation; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ETA, endotracheal aspiration; GVPC, glycine-vancomycin-polymyxin-cycloheximide; HA, haemagglutination assay; HIV, human immunodeficiency virus; hMPV, human metapneumovirus; ICT, immunochromatographic test; IDSA, Infectious Diseases Society of America; IFA, indirect immunofluorescence assay; IGRA, interferon-gamma release assay; IHA, indirect haemagglutination test; ISAGA, immunosorbent agglutination assay; IVIG, intravenous immune globulin; MAG, microparticle agglutination; MAT, micro agglutination test; MERS, Middle East respiratory syndrome; MIC, minimum inhibitory concentration; MIF, microimmunofluorescence assay; MWY, modified Wadowsky Yee agar; MRSA, methicillin-resistant *Staphylococcus aureus*; NIV, non-invasive ventilation; PA, particle agglutination test; PCT, procalcitonin; PCV, pneumococcal conjugate vaccine; PEEP, positive end-expiratory pressure; PPV, pneumococcal polysaccharide vaccine; PSB, protected specimen brush; PSI, pneumonia severity index; RCT, randomized, controlled trial; RR, respiratory rate; RSV, respiratory syncytial virus; SBP, systolic blood pressure; TST, tuberculin skin test; WBC, white blood cell count; WHO, World Health Organization.

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Abstract

Community-acquired pneumonia (CAP) in adults is an infectious disease with high morbidity in China and the rest of the world. With the changing pattern in the etiological profile of CAP and advances in medical techniques in diagnosis and treatment over time, Chinese Thoracic Society of Chinese Medical Association updated its CAP guideline in 2016 to address the standard management of CAP in Chinese adults. Extensive and comprehensive literature search was made to collect the data and evidence for experts to review and evaluate the level of evidence. Corresponding recommendations are provided appropriately based on the level of evidence. This updated guideline covers comprehensive topics on CAP, including aetiology, antimicrobial resistance profile, diagnosis, empirical and targeted treatments, adjunctive and supportive therapies, as well as prophylaxis. The recommendations may help clinicians manage CAP patients more effectively and efficiently. CAP in pediatric patients and immunocompromised adults is beyond the scope of this guideline. This guideline is only applicable for the immunocompetent CAP patients aged 18 years and older. The recommendations on selection of antimicrobial agents and the dosing regimens are not mandatory. The clinicians are recommended to prescribe and adjust antimicrobial therapies primarily based on their local etiological profile and results of susceptibility testing, with reference to this guideline.

KEYWORDS

community-acquired pneumonia, adult, antimicrobial therapy, aetiology, diagnosis, adjunctive therapy, prevention

1 | INTRODUCTION

This guideline is applicable for the immunocompetent community-acquired pneumonia (CAP) patients aged 18 years and older. For immunocompromised patients, such as human immunodeficiency virus (HIV) infection, agranulocytosis, haematological tumour or solid tumour undergoing chemo-radiotherapy, solid organ transplantation and patients receiving glucocorticoid or cytokine antagonist, this guideline may be inappropriate.

2 | METHODOLOGY FOR REVISION OF THE GUIDELINE

The revision of the guideline was initiated by Chinese Thoracic Society (CTS) and Chinese Medical Association (CMA). The overall framework and main content of the updated guideline were finalized following 3 face-to-face work meetings and 2 online video conferences. The experts specialized in methodology provided training on standardized literature search and grading of evidence to all the specialists contributing to the guideline. Level of evidence and grading of recommendation were based on the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines for CAP (2007).[1] The level of evidence represents the assessment on the quality of study evidence, and the grading of recommendation refers to the assessment on the degree to which the benefits of an intervention outweighs the risks. Generally speaking, the higher the evidence level, the stronger the grade of recommendation, but they do not fully correspond to each other. The willingness and values of patients, as well as resource consumption should also be considered when making a recommendation (Table 1).

This guideline document is composed of 8 sections. The core panel members are responsible for 8 separate groups to prepare the first draft by searching and reviewing the relevant domestic and international literature, evaluating evidence level with the unified standard. The grading of recommendations is decided by vote of all members participating in the preparation of the guidelines.

The principal writer was responsible for summarization and modification of the first draft. In the process, 6 face-to-face work meetings were held to discuss revision of the draft. Three rounds of consultation were conducted to solicit advice and opinions from the specialists of the specialty groups within CTS, CMA, specialists in relevant disciplines

TABLE 1 Evidence level and grade of recommendation

Evidence level and grade of recommendation	Description
Evidence level	
Level I (high)	Evidence from well-designed, randomized, controlled trials (RCTs), authoritative guidelines and high quality systematic reviews and meta-analyses
Level II (moderate)	Evidence from RCTs with some limitations (eg, trials without allocation concealment, nonblinded, or loss to follow-up not reported), cohort studies, case series and case-control studies
Level III (low)	Evidence from case reports, expert opinions and in vitro antimicrobial susceptibility studies without clinical data
Grade of recommendation	
A (strong)	Most patients, physicians and policy makers will adopt the recommended action.
B (moderate)	The recommendation will be adopted by the majority, but not by some individuals. Decisions should be made with consideration of the specific condition of the patient to reflect his/her values and willingness.
C (weak)	Insufficient evidence; decisions must be made *via* mutual discussions involving the patients, physicians and policy makers.

such as infectious diseases, clinical microbiology, emergency and critical care medicine and clinical pharmacy and specialists from the United States and Europe. The guideline document was modified for 6 times based on such discussions and feedbacks.

The final revised version was approved by all the writers and consultants.

3 | SECTION 1. DEFINITION AND DIAGNOSIS OF CAP

3.1 | Definition

CAP refers to the infectious inflammation of lung parenchyma (including alveolar wall, ie, pulmonary interstitium in general meaning) acquired outside of hospitals, including pneumonia caused by pathogens with proven latency, the onset of disease is during the latency after the patient is admitted into hospital.

3.2 | Incidence and mortality of CAP in adults

The incidence of CAP in adults is 5–11/1000 person-year in European and North American countries,[2] and increases with age. In the United States, the average incidence of CAP is 2.5/1000 person-year in adult inpatients, 6.3/1000 person-year in the population aged 65 to 79, and the highest 16.4/1000 person-year in the population at least 80 years of age.[3] A Japanese study showed that the incidence of CAP was 3.4/1000, 10.7/1000 and 42.9/1000 person-year in the populations aged 15 to 64, 65 to 74 and $\geq$ 75, respectively.[4] In China, only the proportion of CAP by age group is available at present time, but no specific data are available on the incidence of CAP in adults. A study conducted in China in 2013 showed that in the 16 585 hospitalized CAP patients, much larger proportion was found in $\leq$ 5 years (37.3%) and $>$ 65 years (28.7%) of age groups compared with adults from 26 to 45 years of age (9.2%).[5]

The mortality of CAP increases with age of patient. In Japan, the reported mortality of hospitalized CAP patients was 1.4% in 15–44 years of age group, 3.3% in 45–64 years of age group, 6.9% in 65–74 years of age group and 9.3% in $\geq$75 years of age group.[6] CAP mortality is also associated with the severity of disease. Data from a German CAP surveillance network showed that the 30-day mortality of CAP in adult patients was 8.6%. The mortality rate in outpatients and inpatients was 0.8% and 12.2%, respectively.[7] Additionally, the results of several studies have shown that the 30-day mortality of moderate-to-severe CAP patients was up to 23%-47% in ICU.[8–11]

Currently, we lack the data regarding the incidence and mortality of CAP in China. According to data from the China's Health and Family Planning Statistical Yearbook 2013, in 2008, the two-week prevalence of pneumonia was 1.1‰ in China, slight increase compared with the data in 2003 (0.9‰). In 2012, the average mortality of pneumonia was 17.46/100 000 in China; specifically, 32.07/100 000 in the population under 1 year-old, $<$1/100 000 in the population aged 25 to 39, 23.55/100 000 in the population aged 65 to 69 and up to 864.17/100 000 in the population aged $>$85.[12]

3.3 | Aetiology of CAP in Chinese adults

The distribution and antimicrobial resistance profile of CAP pathogens are significantly different across different countries and regions, and change over time. Currently, the results of several epidemiological surveys of CAP conducted in

Chinese adults have shown that *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* are important pathogens of CAP in adults in China.[13–17] Other common pathogens include *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Klebsiella pneumoniae* and *Staphylococcus aureus*; but *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are infrequently isolated.[13,16–18] In China, only a small number of cases of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) pneumonia are reported in children and teenagers.[19–22] CA-MRSA was not identified in the antimicrobial resistance surveillance of community-acquired respiratory tract pathogens in adults conducted in 2009–2010.[23] For special populations such as elderly patients or patients with underlying diseases (eg, congestive heart failure, cardiovascular or cerebrovascular diseases, chronic respiratory system diseases, kidney failure and diabetes mellitus), gram-negative bacteria such as *K. pneumoniae* and *Escherichia coli* are more common.[18,24,25]

With the development and application of virus detection technology, the role of respiratory tract viruses is gradually gaining attention in the aetiology of CAP in Chinese adults. The results of several recently published multicenter studies showed that the detection rate of viruses was 15%-34.9% in Chinese adult CAP patients, of which influenza virus accounted for the largest proportion. Other contributing viruses included parainfluenza virus, rhinovirus, adenovirus, human metapneumovirus (hMPV) and respiratory syncytial virus (RSV). Among the patients with positive test results for viruses, 5.8%-65.7% could have concomitant infection caused by bacteria or atypical pathogens.[15,18,26,27]

Considering the resistance profile of major pathogens, the high percentage of *S. pneumoniae* resistant to macrolides found in Chinese adult CAP patients is an important characteristic that differs from that in European and American countries. Two nation-wide multicenter surveys on adult CAP conducted in 2003–2005 showed that 63.2%–75.4% of *S. pneumoniae* isolates were resistant to macrolides.[13,17] Recently, the results of 2 multicenter Community-Acquired Respiratory Tract Infection Pathogen Surveillance (CARTIPS) studies in adults conducted in urban tertiary hospitals in China showed that 88.1%–91.3% of *S. pneumoniae* isolates were resistant to azithromycin, the minimum inhibitory concentration of which required to inhibit the growth of 90% of organisms (MIC_{90}) was 32–256 mg/L and 88.2% of the isolates were resistant to clarithromycin.[23,28] While in European and American countries, 12.9%-39% and 4.3%–33.3% of *S. pneumoniae* isolates were resistant to erythromycin and azithromycin, respectively.[19–34] Moreover, 24.5%–36.5% of *S. pneumoniae* isolates were resistant to oral penicillins, and 39.9%-50.7% resistant to second-generation cephalosporins in China. However, relatively low percentage of *S. pneumoniae* isolates were resistant to injectable penicillins and third-generation cephalosporins (1.9% and 13.4%, respectively).[23,28]

The high percentage of *Mycoplasma pneumoniae* strains resistant to macrolides is another important characteristic in the aetiology of CAP in China, which is different from that in most other countries. Study results showed that 58.9%-71.7% of the mycoplasma strains isolated from Chinese adult CAP patients were resistant to erythromycin, and 54.9%-60.4% resistant to azithromycin.[35–37] The infections caused by antibiotic-resistant mycoplasma may prolong the duration of fever and anti-infective treatment.[36] In addition to China, 25%-46% of the mycoplasma strains isolated from Japanese adult and teenage CAP patients were resistant to macrolides. Macrolides-resistant *M. pneumoniae* was also reported in France, Canada, the United States, Spain and Germany.[38–43] *M. pneumoniae* is highly resistant to macrolides in China, but it remains susceptible to doxycycline, minocycline and quinolones.[35,44]

3.4 | Clinical diagnostic criteria for CAP

A. Onset in community.

B. Relevant clinical manifestations of pneumonia: (1) New onset of cough or expectoration, or aggravation of existing symptoms of respiratory tract diseases, with or without purulent sputum, chest pain, dyspnea, or hemoptysis; (2) Fever; (3) Signs of pulmonary consolidation and/or moist rales; (4) Peripheral white blood cell count (WBC) $> 10 \times 10^9$/L or $< 4 \times 10^9$/L, with or without a left shift.

C. Chest radiograph showing new patchy infiltrates, lobar or segmental consolidation, ground-glass opacities, or interstitial changes, with or without pleural effusion.

Clinical diagnosis can be established if a patient satisfies Criterion A, Criterion C and any one condition of Criterion B and meanwhile, tuberculosis, pulmonary tumour, non-infectious interstitial lung disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilia and pulmonary vasculitis are all excluded.

3.5 | Diagnosis and treatment approach of CAP

Step 1: Determine whether a diagnosis of CAP is valid or not. For patients with clinically suspected CAP, the possibility of unusual infections such as tuberculosis and non-infectious causes must be considered.

Step 2: Evaluate the severity of CAP and select the location for treatment.

Step 3: Predict the potential pathogens of CAP and risks of antibiotic resistance (Table 2): considering patient age, season of onset, underlying diseases and risk factors,

TABLE 2 Clinical manifestations of pneumonia in terms of different pathogens

Potential pathogen	Clinical manifestations
Bacteria	Acute onset, high fever with potential shivers, purulent sputum, brown bloody sputum, chest pain, significant increase in peripheral WBC, increased C-reactive protein (CRP), signs of pulmonary consolidation or moist rales; radiograph shows alveolar infiltrates or lobar or segmental distribution of consolidation.[45–49]
Mycoplasma* or *Chlamydia	Under 60 years of age, with few underlying diseases; continuous cough, no sputum or no bacteria discovered in sputum smear test, few pulmonary signs, peripheral WBC $<10 \times 10^9$/L; radiograph may show lesions in the upper lung field of both lungs, centrilobular nodules, tree-in-bud sign, ground-glass opacities, or thickening of bronchial wall and may show signs of consolidation with disease progression.[15,46,50–52]
Virus	Mostly seasonal, may have history of exposure to an epidemic or clustered outbreak, acute upper respiratory tract symptoms, myalgia, normal or decreased peripheral WBC, procalcitonin (PCT) < 0.1 ng/mL, unresponsive to treatment with antibacterial agents; radiograph shows bilateral, interstitial exudates in multiple lobes and/or ground-glass opacities, which may be accompanied by consolidation.[46,53–55]

symptoms or signs, characteristics of chest imaging (X-ray film or CT), laboratory tests, severity of CAP, prior antibacterial therapies and so on.

Step 4: Arrange for reasonable etiological tests, and initiate empirical anti-infective treatment in a timely manner.

Step 5: Evaluate the effectiveness of empirical anti-infective treatment on CAP in a dynamic manner; investigate the cause if initial treatment fails, and adjust treatment protocol promptly.

Step 6: Follow up after treatment; and provide education on health maintenance.

4 | SECTION 2. ASSESSMENT OF CAP SEVERITY, CRITERIA FOR HOSPITAL ADMISSION AND DIAGNOSTIC CRITERIA FOR SEVERE CAP

The evaluation of CAP severity is crucial for selection of appropriate location of treatment, initial empirical antimicrobial agents, as well as adjunctive and supportive treatments.

4.1 | Evaluation of CAP severity

The scoring systems of CAP severity differ from each other (Table 3). They can be used as an aid for evaluation and provide support for clinical diagnosis and treatment, but physicians should take clinical experience into consideration when making judgments, and monitor disease progression in a dynamic manner[56] (II A). CURB-65, CRB-65 (C: disturbance of consciousness, U: urea nitrogen, R: respiratory rate, B: blood pressure, 65: age), and pneumonia severity index (PSI) scoring systems underestimate the risk of death and severity of influenza pneumonia,[57–60] while oxygenation index combined with absolute reduction of peripheral blood lymphocyte is superior to CURB-65 and PSI in predicting the risk of death due to influenza pneumonia[61] (II B).

4.2 | Criteria for hospital admission of CAP patients

CURB-65 score is recommended as a standard for deciding whether a patient should be hospitalized or not. A score of 0–1 point: theoretically, patients should receive outpatient treatment; a score of 2 points: patients are recommended to receive inpatient treatment or extramural treatment with close follow-up; a score of 3–5 points: patients should be hospitalized (I A).

However, other factors such as patient age, underlying diseases, socioeconomic status, gastrointestinal functions and treatment compliance should also be taken into account for comprehensive evaluation[62] (II B).

4.3 | Diagnostic criteria for severe CAP

Criteria for diagnosis of severe CAP[63]: patients who meet any of the major criteria or ≥ 3 minor criteria could be diagnosed as severe pneumonia and need close monitoring and active treatment; it is also recommended that the patients should be hospitalized in ICU if applicable (II A).

4.3.1 | Major criteria

1. Requiring tracheal intubation and mechanical ventilation;
2. Septic shock, and still in need of vasoactive drugs after active fluid resuscitation.

4.3.2 | Minor criteria

1. Respiratory rate (RR) $\geq$30 bpm;
2. Oxygenation index ≤ 250 mm Hg (1 mm Hg = 0.133 kPa);
3. Infiltrates in multiple lung lobes;
4. Disturbance of consciousness and (or) disorientation;

TABLE 3 Features of common scoring scales for evaluating CAP severity

Scales	Indices and calculation	Risk ratings	Recommendation
CURB-65 score[64]	5 indices in total; 1 pt for each criterion satisfied: 1. Disturbance of consciousness; 2. BUN >7 mmol/L; 3. RR ≥ 30 bpm; 4. SBP < 90 mm Hg or DBP ≤ 60 mm Hg; 5. age ≥ 65 yrs.	Mortality risk evaluation: 0–1: low risk; 2: moderate risk; 3–5: high risk	Simple, highly sensitive, easy for clinical application
CRB-65 score[64]	4 indices in total; 1 pt for each criterion satisfied: 1. Disturbance of consciousness; 2. RR ≥ 30 bpm; 3. SBP < 90 mm Hg or DBP ≤ 60 mm Hg; 4. age ≥ 65 yrs.	Mortality risk evaluation: 0: low risk, outpatient treatment; 1–2: moderate risk, hospital admission or extramural treatment with close follow-up is recommended; ≥3: high risk, patient should be hospitalized	Suitable for medical institutions unable to perform biochemical tests
PSI score[65]	Sum of age (female minus 10 pts) and scores for all risk factors: 1. Residing in a geracomium (+10 pts); 2. Underlying disease: tumour (+30 pts); hepatic disease (+20 pts); congestive heart failure (+10 pts); cerebrovascular disease (+10 pts); renal disease (+10 pts); 3. Physical signs: change in state of consciousness (+20 pts); RR ≥ 30 bpm (+20 pts); SBP < 90 mm Hg (+20 pts); body temperature < 35°C or ≥ 40°C (+15 pts); heart rate ≥ 125 bpm (+10 pts); 4. Laboratory tests: arterial blood pH < 7.35 (+30 pts); BUN ≥30 mg/dL (or 11 mmol/L) (+20 pts); blood sodium < 130 mmol/L (+20 pts); blood glucose ≥ 14 mmol/L (+10 pts); Haematocrit (Hct) < 30% (+10 pts); PaO_2 < 60 mm Hg (or fingertip O_2 saturation < 90%) (+10 pts); 5. Chest radiograph: pleural effusion (+10 pts).	Evaluation of mortality risk: Low risk: Class I (<50 years of age, without underlying diseases); Class II (≤70 pts); Class III (71–90 pts); Moderate risk: Class IV (91–130 pts); High risk: Class V (>130 pts). Patients at Classes IV and V need hospitalization	Sensitive measurement for evaluating whether a patient needs hospitalization, highly specific. Complex scoring system
CURXO score[66]	Major indices: 1. Arterial blood pH < 7.30; 2. SBP < 90 mm Hg. Minor indices: 1. RR ≥ 30 bpm; 2. Disturbance of consciousness; 3. BUN > 11 mmol/L; 4. PaO_2 < 54 mm Hg or oxygenation index < 250 mm Hg; 5. Age ≥ 80 yrs; 6. Chest X-ray showing multiple-lobe or bilateral pulmonary involvement.	Patients are diagnosed as severe CAP if any one of the major indices or two of the minor indices are met	Simple scoring method used for emergency diagnosis of severe CAP
SMART-COP Score[67]	Sum of scores for all the following risk factors: SBP < 90 mm Hg (+2 pts); chest X-ray showing bilateral pulmonary involvement (+1 pt); serum albumin < 35 g/L (+1 pt); RR ≥ 30 bpm (> 50 yo) or ≥ 25 bpm (≤ 50 yo) (+1 pt); heart rate ≥ 125 bpm (+1 pt); New onset of disturbance of consciousness (+1 pt); hypoxemia (+2 pts): PaO_2 < 70 mm Hg, or fingertip O_2 saturation ≤ 93%, or oxygenation index < 333 mm Hg (≤ 50 yo); PaO_2 < 60 mm Hg, or fingertip O_2 saturation ≤ 90%, or oxygenation index < 250 mm Hg (>50 yo); arterial blood pH < 7.35 (+2 pts).	0–2: low risk 3–4: moderate risk 5–6: high risk 7–8: extremely high risk	A score > 3 indicates the possibility that the patient needs respiratory monitoring or circulatory support therapy

5. Blood urea nitrogen (BUN) $\geq$ 7.14 mmol/L;
6. Systolic blood pressure (SBP) $<$ 90 mm Hg, requiring active fluid resuscitation.

5 | SECTION 3. ETIOLOGICAL DIAGNOSIS OF CAP

5.1 | Selection of method for etiological diagnosis of CAP

1. Unless there is a clustered outbreak of pneumonia or the clinical response to initial empirical treatment is inadequate, etiological tests are generally not required for outpatients with mild CAP[1,2,68–70] (III B).
2. Hospitalized CAP patients (including patients who require monitoring at the emergency room) usually require etiological testing. The selection of etiological tests should be based on multiple factors, including patient age, underlying diseases, immune status, clinical characteristics, severity of disease and prior anti-infective treatment. Appropriate etiological testing is especially important when antimicrobial adjustment is necessary due to insufficient efficacy of empirical anti-infective treatment[1,2,68] (I A).
3. See Table 4 for the recommended etiological tests of CAP under specific clinical situations.
4. Invasive etiological sampling is only selectively applicable for the following patients:
    i. Patients with pneumonia and concomitant pleural effusion, especially when pleural effusion is on the same side of the infected pulmonary lesion; etiological testing could be performed with pleural effusion samples collected *via* thoracentesis.
    ii. Patients receiving mechanical ventilation: etiological testing could be performed with lower respiratory tract samples obtained *via* bronchoscopy, including endotracheal aspiration (ETA), bronchoalveolar lavage fluid (BALF) and protected specimen brush (PSB).
    iii. Patients who have inadequate response to empirical treatment and are suspected to be infected with unusual pathogens: when the cause of disease cannot be determined with respiratory tract samples obtained with regular methods, etiological testing could be performed with lower respiratory tract samples obtained *via* bronchoscopy (including ETA, BALF and PSB) or histological samples obtained *via* percutaneous needle lung biopsy.
    iv. Patients without improvement after active anti-infective therapies, who require differential diagnosis with non-infectious pulmonary lesions (such as tumour, vasculitis and interstitial lung disease) (III B).

5.2 | Primary testing methods for CAP pathogens and diagnostic criteria

See Table 5 for the primary testing methods for CAP pathogens and their corresponding diagnostic criteria.

6 | SECTION 4. ANTI-INFECTIVE THERAPIES FOR CAP

6.1 | Empirical anti-infective therapies for CAP

After clinical diagnosis of CAP is established, and etiological test and sampling arranged appropriately, the most potential pathogens should be assessed in terms of patient age, underlying disease, clinical characteristics, results of laboratory and radiography tests, severity of disease, hepatic and renal functions, and history of medication and antimicrobial susceptibility profile, then evaluate the risk for antibiotic resistance, select the appropriate anti-infective agent (s) and dosing regimen (Table 6). The initial empirical antibacterial therapy should be administered promptly. It is important to note that the epidemiological distribution and antimicrobial resistance profile of pathogens may be different in different regions of China. The anti-infective drugs listed in Table 6 are optional for initial empirical therapy. The treatment recommendations are only theoretical. The selection of therapies for specific patients must be based on the actual situation in local healthcare facilities.

Additionally, the pharmacokinetic and pharmacodynamic properties of antibacterial agents must be taken into consideration. For time-dependent antibacterial agents (such as penicillins, cephalosporins, monobactams and carbapenems), their bactericidal ability is almost saturated at 4–5 times of MIC,[115] and T $>$ MIC (time above MIC) is an important determinant of efficacy.[116] Better clinical efficacy can be achieved by multiple doses per day based on half-lives. Meanwhile, the bactericidal ability of concentration-dependent antibacterial agents, such as aminoglycosides and quinolones, increases with drug concentration. The effect improves with higher peak drug concentration.[116] Therefore, these drugs are usually administered once daily in order to increase drug activity and decrease the risk of drug resistance and kidney injury caused by aminoglycosides.

Recommendations of this guideline for empirical anti-infective treatment of CAP are provided in the following.

1. The first dose of anti-infective agent should be used as early as possible after diagnosis of CAP is established in

TABLE 4 Recommended etiological tests for CAP under specific clinical situations

Clinical conditions	Sputum smear and culture[a]	Blood culture[b]	Pleural effusion culture	*Mycoplasma*/ *Chlamydia*/ *Legionella* screening[c]	Respiratory tract virus screening[d]	LP1 urinary antigen[e]	SP urinary antigen[f]	Fungal antigen	Tuberculosis screen g
Clustered outbreak[2]				√	√	√			
Inadequate response to initial empirical therapy[1]	√	√		√	√	√	√		
Severe CAP[1,2,68]	√	√		√	√	√	√		
Unusual radiographic manifestations[1,2,52,71–76]									
1. Necrotizing pneumonia or concomitant cavity	√[i]	√						√	√
2. Concomitant pleural effusion	√	√	√	√		√	√		√
3. Lesions in multiple lobes of both lungs	√	√		√	√	√			√
Underlying disease									
1. Concomitant chronic obstructive pulmonary disease[1,2,24,25,77]	√								
2. Concomitant structural lung disease[1,25]	√								√
3. Immunodeficiency[h78–80]	√	√		√	√	√	√	√	√
History of travel within 2 weeks before onset of disease[j1,2]						√			

[a]Other than sputum, acceptable samples also include lower respiratory tract samples and histological biopsy samples such as ETA (endotracheal aspiration), BALF (bronchoalveolar lavage fluid) and PSB (protected specimen brush).

[b]Blood culture should include aerobic and anaerobic bacterial cultures.

[c]*Mycoplasma*, *Chlamydia* and *Legionella* screen items are nucleic acid and serum specific antibodies.

[d]Screening tests are for nucleic acid, antigens, or serum specific antibodies of respiratory tract viruses.

[e]LP1: *Legionella pneumophila* serogroup 1.

[f]SP, *Streptococcus pneumoniae*.

[g]Tuberculosis screening prefers sputum smear for the test of acid-fast bacteria. Mycobacteria culture and nucleic acid detection should be performed if applicable.

[h]For immunodeficient patients, in addition to the relatively comprehensive etiological tests listed in this table, patients should also be screened for opportunistic pathogens, such as *Pneumocystis jiroveci* pneumonia, cytomegalovirus and nontuberculous mycobacteria.

[i]Sputum smears should be used to discover bacteria and fungi, while bacterial and fungal cultures should be conducted simultaneously.

[j]Patients with history of travel to special epidemic regions should also be screened for corresponding respiratory tract contagious diseases.

TABLE 5 Primary testing methods for CAP pathogens and implications for diagnosis

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
Aerobic bacteria and facultative anaerobic bacteria	Direct smear microscopy (Gram staining) Regular culture	Sputum, ETA, BALF and PSB samples; blood, pleural effusion and bronchial mucosa biopsy samples; lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) The pathogen is found in cultures of blood or other sterile samples (such as pleural effusion, lung biopsy samples, etc.)[81]; (2) *Francisella tularensis*, *Yersinia pestis* or *Bacillus anthracis* isolated from qualified lower respiratory tract samples; (3) Positive result for *S. pneumoniae* urinary antigen test (ICT) (except for children)[81–83] 2. Test results that are important reference for etiological diagnosis: (1) Significant growth of dominant bacteria ($\geq$ +++) in qualified lower respiratory tract samples (except for normal colonization flora); (2) Small amount of bacterial growth in qualified lower respiratory tract samples, but results are consistent with smear microscopy results (*S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*); (3) Apparent bacterial phagocytosis by neutrophils could be seen in smear microscopy of qualified lower respiratory tract samples	For qualified lower respiratory tract samples, sputum samples must meet the following conditions: squamous cells < 10 per low-power field; polymorphonuclear leukocytes >25 per low-power field, or the ratio between the two is <1:2.5[84]
	S. pneumoniae urinary antigen (ICT)	Fresh urine		
Anaerobic bacteria	Direct smear microscopy (Gram staining) Anaerobial cultures	Blood, pleural effusion	Test results that can be used as evidence for etiological diagnosis: The pathogen is found in cultures of blood or other sterile samples (such as pleural effusion, lung biopsy samples, etc.)	
Mycobacteria	Smear microscopy (microscopy with Ziehl-Neelsen staining, fluorescence microscopy) Mycobacterial culture Nucleic acid detection (simultaneous mycobacteria culture is recommended)	Sputum, ETA, BALF and PSB samples; blood, pleural effusion, bronchial mucosa biopsy samples; lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) Acid-fast bacilli discovered in smear microscopy, but cannot differentiate between tuberculosis mycobacteria or non-tuberculosis mycobacteria[85,86]; (2) A positive result for acid-fast bacillus culture, and can differentiate between tuberculosis mycobacteria or non-tuberculosis mycobacteria 2. Test results that are important references for etiological diagnosis: A positive result for mycobacteria nucleic acid detection, and can differentiate between tuberculosis mycobacteria or non-tuberculosis mycobacteria[85,87]	1. Fluorescent smear microscopy is more sensitive than Ziehl-Neelsen staining[85,86] 2. The sensitivity of mycobacteria culture is superior to that of smear microscopy; in vitro susceptibility testing can be performed, but it is more time-consuming and complex, and has a higher biological safety requirement for laboratories[85,86] 3. Xpert MTB/RIF is the method recommended by WHO for testing mycobacteria. It can provide information on rifampin resistance simultaneously[85,87]. Currently, the commercial kit has been approved by the CFDA
	IGRA TST	Whole blood samples		

(Continues)

TABLE 5 (Continued)

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
				4. A positive result for IGRAs indicates that the host has been sensitized by tuberculosis mycobacteria antigens; a positive result for TST indicates previous infection of tuberculosis, which is not recommended for diagnosis of active tuberculosis according to the WHO[85,88,89]
Legionella	Serum specific antibody assay (IFA, ELISA) *Legionella pneumophila* Type I urinary antigen assay (ICT) Nucleic acid assay Isolation and culture (BCYE nutrient culture medium, GVPC and MWY screening culture medium) Antigen assay in lower respiratory tract samples (DFA)	Two sets of serum samples from acute phase and recovery phase Urine Sputum, ETA, BALF and PSB samples; blood, pleural effusion, bronchial mucosa biopsy samples; lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) *Legionella* is isolated from cultures of qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples[81,90–94]; (2) A positive result for *L. pneumophila* serotype I urinary antigen assay (ICT)[90–94]; (3) Serum *L. pneumophila* Type I-specific antibody titer (IFA or ELISA) shows a 4-fold or higher change between the two sets of serum samples from acute phase and recovery phase[90–94] 2. Test results that are important reference for etiological diagnosis: (1) Serum *L. pneumophila* serotype I-specific antibody titer in a single sample reaches the criteria for a positive result[90–94]; (2) Serum specific antibody titer of other serum types of *Legionella* or other *Legionella* strains besides *L. pneumophila* serotype I showing 4-fold or higher increase[90–94]; (3) A positive result for *L. pneumophila* antigen assay in qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples (DFA)[90–94]; (4) A positive result for *Legionella* nucleic acid assay in qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples (DFA)[90–95]	1. A positive result for *Legionella* culture is the gold standard for diagnosis of *Legionella* infection. However, the positive rate is low, and prior use of anti-infective drugs can cause a false positive result[90]; BALF and lung biopsy samples can increase the positive rate 2. *L. pneumophila* serotype I urinary antigen assay can be used for rapid diagnosis at early stage, and the results are not affected by prior anti-infective therapies [90,96] 3. Although *Legionella* antigen assay in qualified lower respiratory tract samples can be fast and convenient, and can provide differentiation between strains and subtypes, its sensitivity and specificity are not satisfying[90–94] 4. *Legionella* nucleic acid assay can be used for early-stage diagnosis of *Legionella* pneumonia; it is highly sensitive, and can detect the subtypes of *L. pneumophila*.[90] However, this test has not been accepted in the United States and Europe as a criteria for definite diagnosis.[91–94]

(Continues)

TABLE 5 (Continued)

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
Mycoplasma pneumoniae	Serum specific antibody assays (CF, PA, MAG, EIA, IFA) Nucleic acid assay Culture (special medium)	Two sets of serum samples from acute phase and recovery phase Oropharyngeal swabs; nasopharyngeal swabs; sputum, ETA, BALF and PSB samples; blood, pleural effusion, bronchial mucosa biopsy samples; lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) *M. pneumoniae* is isolated from cultures of oropharyngeal or nasopharyngeal swabs, qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples[81,97]; (2) Serum *M. pneumoniae* - specific antibody titer shows a 4-fold or higher change between the two sets of serum samples from acute phase and recovery phase[81,97] 2. Test results that are important reference for etiological diagnosis: (1) A positive result for *M. pneumoniae* nucleic acid detection in oropharyngeal or nasopharyngeal swabs, qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples[81,95]; (2) A positive result for *M. pneumoniae*-specific IgM antibody in a single set of serum sample[97]	1. A positive result for *M. pneumoniae* culture can be used to establish definite diagnosis, but the test is time-consuming, and the positive rate is relatively low[98] 2. Serum specific antibody titer obtained *via* CF or PA methods is largely affected by IgG, so its value for early-stage diagnosis is limited. MAG, EIA and IFA methods can detect serum specific IgM or IgG. Serum specific IgM appears earlier, but acute infection could not be excluded by a negative result. A quadruple or higher increase in specific antibodies across two sets of serum samples is relevant for retrospective diagnosis[98] 3. *M. pneumoniae* nucleic acid assay has been approved for clinical use as an important tool for rapid early-stage diagnosis[81,95]
Chlamydia pneumoniae	Serum specific antibody detection (MIF) Nucleic acid detection Culture (cell culture)	Two sets of serum samples from acute phase and recovery phase Oropharyngeal swabs; nasopharyngeal swabs; sputum, ETA, BALF and PSB samples; blood, pleural effusion, bronchial mucosa biopsy samples; lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) *C. pneumoniae* is isolated from cultures of oropharyngeal or nasopharyngeal swabs, qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples[81,99,100]; (2) Serum *C. pneumoniae*-specific IgG antibody titer (MIF method) shows a 4-fold or higher change between the two sets of serum samples from acute phase and recovery phase[99,100]; (3) Serum *C. pneumoniae*-specific IgM (MIF method) $\geq$ 1:16[99,100] 2. Test results that are important reference for etiological diagnosis: (1) A positive result for *C. pneumoniae* nucleic acid assay in oropharyngeal or nasopharyngeal swabs, qualified lower respiratory tract samples, pleural effusion, bronchial mucosa biopsy samples, or lung biopsy samples.[81,95] (2) Serum *C. pneumoniae*-specific IgG titer (MIF) in a single set of serum samples $\geq$ 1:512.[99,100]	1. *C. pneumoniae* is an obligate intracellular pathogen, which can only be isolated in vitro *via* cell culture with complex technique. The method is generally not recommended for clinical diagnosis[99,100] 2. Serum specific antibody assay has limited value for early-stage diagnosis; an increase in specific IgM, or a quadruple or higher increase in IgG titer across two sets of serum samples is relevant for retrospective diagnostic[99,100]

(Continues)

TABLE 5 (Continued)

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
				3. *C. pneumoniae* nucleic acid assay has been approved for clinical use; a positive result has important value for rapid early-stage diagnosis[81,95]
Coxiella burnetii	Nucleic acid assay Serum specific antibody assays (CF, MAT, IFA, ELISA) Histopathological examination	Pharyngeal swabs; nasal swabs; sputum, ETA, BALF and PSB samples Two sets of serum samples from acute phase and recovery phase Lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) *C. burnetii* is isolated from cultures of oropharyngeal or nasopharyngeal swabs or qualified lower respiratory tract samples[94]; (2) A positive result for *C. burnetii* nucleic acid assay in oropharyngeal or nasopharyngeal swabs or qualified lower respiratory tract samples[91,94]; (3) *C. burnetii* is found in immunohistochemical staining of lung biopsy samples, with relevant inflammatory reactions[91,94]; (4) Serum *C. burnetii* Phase II-specific IgG antibody titer (MIF method) shows a 4-fold or higher change between the two sets of serum samples from acute phase and recovery phase.[91,94] 2. Test results that are important reference for etiological diagnosis: (1) Serum *C. burnetii* Phase II-specific IgG (MIF) in a single set of serum samples $\geq$ 1:128 (IFA), or results by ELISA, dot-ELISA, MAT, or CF shows an increase in serum *C. burnetii* Phase II-specific antibodies (IgG, IgM or complement-fixing antibody) titer in a single set of serum samples.[91,94]	1. A definite diagnosis of Q fever pneumonia can be established if *C. burnetii* is isolated from cultures of qualified lower respiratory tract samples or if *C. burnetii* is found in immunohistochemical staining of lung biopsy samples,[91,94] but the sensitivity of the tests is relatively low. 2. A positive result for *C. burnetii* nucleic acid assay in oropharyngeal or nasopharyngeal swabs or qualified lower respiratory tract samples has been listed as evidence for definite diagnosis of Q fever pneumonia by the United States and Europe. The test is an important tool for rapid early-stage diagnosis.[91,94] 3. Serum *C. burnetii* Phase II-specific IgM antibody assay is helpful for early-stage diagnosis.[91,94]
Virus	Nucleic acid assay Viral antigen assay (DFA, colloidal gold method) Serum specific antibody assays (IFA, ELISA, CF, haemagglutination inhibition assay)	Respiratory tract samples such as oropharyngeal swabs, nasopharyngeal swabs, nasopharyngeal aspirate, airway aspirate and sputum Two sets of serum samples from acute phase and recovery phase	1. Test results that can be used as evidence for etiological diagnosis: (1) A positive result for nucleic acid assay of influenza virus, parainfluenza virus Types 1–4, RSV, adenovirus, coronavirus, hMPV and so on in oropharyngeal or nasopharyngeal swabs, qualified lower respiratory tract samples, or lung tissue samples[81,95,101,102]; (2) Serum specific IgG antibody titer of a respiratory tract virus such as influenza virus or RSV shows a 4-fold or higher change between the two sets of serum samples from acute phase and recovery phase[101–103]; (3) A positive result for rapid antigen assay of influenza virus (DFA, colloidal gold method) in oropharyngeal or nasopharyngeal swabs or qualified lower respiratory tract	1. A positive result for viral isolation and culture is the gold standard for diagnosis of respiratory tract viral infection. It has important value for the discovery and diagnosis of pathogens of respiratory contagious disease with new or sudden onset. However, the test is relatively time-consuming, and requires better laboratory

(Continues)

TABLE 5 (Continued)

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
	Viral isolation and culture	Fresh respiratory tract samples such as oropharyngeal swabs, nasopharyngeal swabs, nasopharyngeal aspirate, airway aspirate and sputum	samples, with supporting relevant epidemiological history[101,102]; (4) A positive result for rapid antigen assay of parainfluenza virus Types 1–4, RSV, adenovirus, coronavirus, or hMPV (DFA) in oropharyngeal or nasopharyngeal swabs or qualified lower respiratory tract samples[81]; (5) A respiratory tract virus such as influenza virus or RSV is isolated from qualified lower respiratory tract samples 2. Test results that are important reference for etiological diagnosis: A positive result for specific IgM of respiratory tract viruses such as influenza virus or RSV.[101–103]	conditions, so it is not a regular test for clinical setting.[81,101,102] 2. The sensitivity and specificity of real-time PCR/rRT-PCR (real-time reverse transcriptase PCR) are relatively high. It is a preferred method for rapid diagnosis of respiratory tract infection with influenza virus, avian influenza virus and so on.[81,95,101,102] 3. Viral antigen assay in qualified lower respiratory tract samples can be used as an initial screening method for rapid early-stage diagnosis. It is less sensitive than nucleic acid assay. Patient's epidemiological history and clinical symptoms should be taken into account when interpreting the results. Nucleic acid assay or viral isolation and culture can be performed for further validation if necessary[101,102] 4. Serum specific viral antibody assay is the main method for retrospective diagnosis[101,102]
Fungus	Smear microscopy (Gram staining, microscopy with KOH as floating fluid, Giemsa staining, GMS staining, mucicarmine staining)	Sputum, ETA, BALF and PSB samples; bronchial mucosa biopsy samples or lung biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) Fungus found in cultures of blood or other sterile samples (such as pleural effusion, lung biopsy tissue samples, etc.) (note that samples with positive result of *Aspergillus* in blood culture due to contamination should be excluded) [81,104]; (2) *Cryptococcus*, mycelial fungus, or human *Pneumocystis* found in immunohistochemical staining of lung tissue samples, with corresponding inflammatory reactions[91,94,104]; (3) *Cryptococcus* or human *Pneumocystis* found in smear microscopy of qualified lower respiratory tract samples [81,105]; (4) *Cryptococcus neoformans* isolated from culture of qualified lower respiratory tract samples[105,106]; (5) A positive result for serum cryptococcal capsular polysaccharide antigen[107]	1. Besides regular Gram stain microscopy, mucicarmine staining can also be used for detection of *Cryptococcus*. GMS staining can be used for detection of human *Pneumocystis*. Microscopy with KOH as floating fluid can be used to detect hypha and spores of fungi, but the strain of fungi cannot be differentiated 2. A positive result for the culture of a sample from a usually
	Fungal culture	Sputum, ETA, BALF and PSB samples; pleural effusion, bronchial mucosa biopsy samples; lung biopsy samples, blood		
	1–3-β-D glucan antigen	Serum		

(Continues)

TABLE 5 (Continued)

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
	Galactomannan antigen	Serum, BALF	2. Test results that are important reference for etiological diagnosis: (1) A positive result for serum or BALF galactomannan antigen; (2) A positive result for 1–3-β-D glucan antigen, with exclusion of factors that can potentially cause a false positive result	sterile site using an aseptic technique is the gold standard of diagnosis; for non-sterile samples, the possibility of colonization or pollution should be carefully excluded 3. Serum 1–3-β-D glucan antigen assay has some value for the diagnosis of invasive fungal infection, except for *Cryptococcus* and *Zygomycetes* [105,107,108]; serum or BALF galactomannan antigen assay has important value for the diagnosis of invasive aspergillosis.[105,107,109] 4. There is possibility of false negative for serum cryptococcal capsular polysaccharide antigen assay in patients with non-disseminated cryptococcosis. The studies currently available do not support the test to be used for efficacy evaluation and prognosis prediction[107] 5. Although a positive result for cryptococcal capsular polysaccharide antigen in cerebrospinal fluid is not direct evidence for diagnosis of pulmonary cryptococcosis, physicians should be alert to the possibility of concomitant cryptococcosis for patients with positive results of cryptococcal capsular polysaccharide antigen in cerebrospinal fluid
	Cryptococcal capsular polysaccharide antigen (latex agglutination method, EIA)	Serum, cerebrospinal fluid		
	Histopathological examination	Lung biopsy samples		
Parasite	Smear or tissue smear microscopy	Sputum or other lower respiratory tract samples, pleural effusion, lung tissue biopsy samples	1. Test results that can be used as evidence for etiological diagnosis: (1) Parasite body, eggs, trophozoite, cysts, or oocysts found in smear microscopy of qualified respiratory tract samples[81,110]; (2) Parasite eggs, body, trophozoite, cysts, or oocysts found in	1. Eggs of *Paragonimus* and trophozoite of amebic protozoa could be detected in direct smear microscopy. Trophozoite

(Continues)

TABLE 5 (Continued)

Pathogen	Testing method	Samples used	Implication for diagnosis	Description
	Histopathological examination	Lung tissue biopsy samples	immunohistochemical staining of lung tissue samples[81,110]; (3) A positive result for nucleic acid assay of *Toxoplasma gondii* in blood, cerebrospinal fluid, or qualified respiratory tract samples or lung tissue samples[81,111]; a positive result for nucleic acid assay of *Enterocytozoon bieneusi, Cryptosporidium* and so on in blood, cerebrospinal fluid, or qualified respiratory tract samples or lung tissue samples[81]; (4) A positive result for circulating parasitic antigen in blood or other body fluids[110] 2. Test results that are important reference for etiological diagnosis: (1) A positive result for intradermal test with parasitic antigens[110]; (2) A positive result for corresponding serum specific antibodies of a parasite (IgG, IgM or IgA) [81,110,111]	or cysts of *Toxoplasma gondii* could be detected by Giemsa staining, and oocysts of *Cryptosporidium* by modified acid-fast staining; *Enterocytozoon bieneusi* by modified three-color staining[81] 2. If an opportunistic parasitic infection such as toxoplasmosis is suspected in an immunodeficient patient, nucleic acid assay can be selected as a primary testing method to obtain rapid early-stage diagnosis[112–114] 3. For immunocompetent patients, serum specific antibody assay is the most commonly used initial screening test for parasitic infections. However, since serum specific antibodies continue to exist for a long time after onset of parasitic infections, a positive result for an intradermal test with parasitic antigens or a positive result for serum specific antibodies (IgG, IgM or IgA) does not necessarily indicate acute infection[110,111]
	Nucleic acid assay	Blood, cerebrospinal fluid, BALF, bronchial mucosa or lung biopsy samples		
	Serum specific antibody assays (DT, ELISA, IFA, HA, IHA, ISAGA, Western blot)	Serum		
	Antigen assays (ELISA, ICT)	Blood, cerebrospinal fluid, pleural effusion and so on.		

Abbreviations: BALF, bronchoalveolar lavage fluid; BCYE, buffered charcoal-yeast extract; CF, complement fixation test; CFDA, China Food and Drug Administration; DFA, direct fluorescent antibody test; DT, Sabin-Feldman dye test; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; ETA, endotracheal aspirate; Giemsa, Giemsa staining; GMS, Gomori Methenamine Silver; GVPC, glycine-vancomycin-polymyxin-cycloheximide; HA, haemagglutination assay; hMPV: human *Metapneumovirus*; ICT, immunochromatographic test; IFA, indirect immunofluorescence assay; IGRA, interferon-gamma release assay; IHA, indirect haemagglutination test; ISAGA, immunosorbent agglutination assay; KOH, potassium hydroxide; MAG, microparticle agglutination; MAT, micro agglutination test; MIF, microimmunofluorescence assay; MWY, modified Wadowsky Yee agar; PA, particle agglutination test; PSB, protected specimen brush; RSV, respiratory syncytial virus; TST, tuberculin skin test; WHO, World Health Organization.

order to improve efficacy and decrease mortality and hospital stay. However, it is important to note that a correct diagnosis is a prerequisite. Physicians should not ignore necessary differential diagnosis for the purpose of early diagnosis[117–120] (II B).

2. For mild CAP outpatients, oral anti-infective agents with high bioavailability should be used when possible. Oral treatment with amoxicillin or amoxicillin-clavulanic acid is recommended[2,121,122] (I B). For young patients without underlying diseases, oral doxycycline or minocycline may be considered if suspected of mycoplasma or chlamydia infection[1,123] (III B). *S. pneumoniae* and *M. pneumoniae* are highly resistant to macrolides in China.[28,36] Empirical macrolides treatment can only be used in regions with lower resistance rates[122] (II B). Respiratory quinolones can be used instead in regions with higher resistance rates to macrolides or in patients who are hypersensitive or intolerant to the drugs mentioned above[121,122,124] (II B).
3. For CAP patients who require hospitalization, β-lactams monotherapy or in combination with doxycycline, minocycline or macrolides and respiratory quinolones monotherapy are recommended[2,125–127] (II B). However, compared with combination therapies, respiratory quinolones monotherapy is associated with fewer adverse reactions,[128] and no skin test is required.
4. For young adult patients with severe CAP and without underlying diseases who require admission to ICU, penicillins-lactamase inhibitor combinations, third generation cephalosporins, ertapenem combined with macrolides or respiratory quinolones monotherapy are recommended.[1,2,127,129–132] For the elderly patients or patients with underlying diseases, combination antimicrobial therapy is recommended[133] (II B).
5. For CAP patients at risk of aspiration, the optimal selection should be drugs with anti-anaerobic activity, such as ampicillin-sulbactam, amoxicillin-clavulanic acid, moxifloxacin, carbapenems and so on, or therapies in combination with metronidazole, clindamycin and so on [134–141] (II A).
6. For hospitalized patients ≥ 65 years of age and with underlying diseases (eg, congestive heart failure, cardiovascular and cerebrovascular diseases, chronic respiratory system diseases, kidney failure, diabetes mellitus, etc.), the possibility of *Enterobacteriaceae* infection should be considered.[24] Such patients should be further evaluated for the risk of infections with extended-spectrum beta-lactamases (ESBLs) -producing bacteria (eg, history of colonization or infection with ESBLs-producing bacteria, prior use of third generation cephalosporins, history of repeated or long-term hospitalization, indwelling implants, renal replacement therapies).[142–144] Cephamycins,[145,146] piperacillin-tazobactam, cefoperazone-sulbactam or ertapenem can be used in empirical therapy for high-risk patients [24,147] (III B).
7. During influenza seasons, CAP patients with suspected influenza virus infection are recommended to receive regular influenza virus antigen test or nucleic acid assay. Proactive antiviral therapy with neuraminidase inhibitors should be administered simultaneously even 48 h after disease onset. It is not necessary to wait for the results of influenza pathogen tests[148–152] (I A). During influenza seasons, physicians must be aware of the possibility of secondary bacterial infections, especially *S. pneumoniae*, *S. aureus* and *H. influenzae*, which are relatively common[153–155] (II A).
8. Anti-infective therapy can usually be terminated 2–3 days after fever is relieved and the primary respiratory tract symptoms are improved significantly. However, the duration of therapy should differ based on the severity of disease, treatment response, complications and pathogens. It is not necessary to use chest X-ray or CT as an indication of termination of anti-bacterial agents. Generally, the duration of therapy should be 5–7 days for patients with mild or moderate CAP, which could be reasonably prolonged for patients with severe CAP or with extra-pulmonary complications. The duration of therapy can be prolonged to 10–14 days for patients with atypical pathogens and/or slow response to treatment. *S. aureus*, *P. aeruginosa*, *Klebsiella* and anaerobic bacteria may cause necrosis of lung tissues, therefore, the duration of therapy may be prolonged to 14–21 days[1,2,122,156–159] (I B).

6.2 | Targeted anti-infective therapies for CAP

Once aetiology of CAP is determined, targeted therapies can be delivered according to the results of in vitro susceptibility testing. See Table 7 for common pathogens of CAP, common anti-infective agents, as well as dosage and administration.

7 | SECTION 5. ADJUNCTIVE THERAPIES FOR CAP

CAP is the primary cause of death among infectious diseases. In addition to anti-infective treatment targeting the pathogens, it is also necessary for patients with moderate or severe CAP to receive adjunctive therapies such as rehydration, maintenance of fluid and electrolyte balance, nutrition support and physical therapy[2] (II B). For patients with concomitant low blood pressure, early fluid resuscitation is an important measure to decrease the mortality of serious CAP[1,168] (II B). For patients with hypoxemia, oxygen

TABLE 6 Selection of anti-infective agents for initial empirical therapy

Populations	Common pathogens	Anti-infective agents for initial empirical therapy	Comment
Outpatient treatment (Oral administration is recommended)			
Young adults without underlying disease(s)	*S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, influenza virus, adenovirus, *M. catarrhalis*	(1) Aminopenicillins, penicillins-β-lactamase -inhibitor combinations; (2) I or II generation cephalosporins; (3) doxycycline or minocycline; (4) respiratory quinolones; (5) macrolides	(1) Differentiate among bacterial pneumonia, *Mycoplasma*, *Chlamydia* and viral pneumonia based on clinical characteristics; (2) Mild pneumonia caused by *Mycoplasma*, *Chlamydia* and virus is usually self-limited
Patients with underlying disease(s) or elderly patients (age ≥ 65 years)	*S. pneumoniae*, *H. influenzae*, *Enterobacteriaceae* such as *K. pneumoniae*, *C. pneumoniae*, influenza virus, RSV, *M. catarrhalis*	(1) Penicillins-β-lactamase-inhibitor combinations; (2) II or III generation cephalosporins (oral); (3) respiratory quinolones; (4) penicillins-lactamase -inhibitor combinations, II generation cephalosporins, III generation cephalosporins combined with doxycycline or minocycline or macrolides	Monotherapy with doxycycline or minocycline or macrolides is not recommended in patients with risk factors of resistant *S. pneumoniae* (1), such as age > 65 years, underlying diseases (chronic cardiac, pulmonary, or renal diseases, diabetes mellitus and immunosuppression), alcoholism and β-lactams treatment within 3 months.
Inpatient treatment, non-ICU (Intravenous or oral administration)			
Young adults without underlying disease(s)	*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *M. pneumoniae*, *C. pneumoniae*, influenza virus, adenovirus, other respiratory tract viruses	(1) Penicillin G, aminopenicillins, penicillins-β-lactamase-inhibitor combinations; (2) II or III generation cephalosporins, cephamycins, oxacephems; (3) the above drugs combined with doxycycline, minocycline or macrolides; (4) respiratory quinolones; (5) macrolides	(1) Only 1.9% the *S. pneumoniae* isolates from adult CAP are resistant to intravenous penicillins in China. The percentage of intermediate strains is only about 9%. Intravenous penicillins are still effective in hospitalized patients infected with penicillin-intermediate *S. pneumoniae* when increasing the dosage[23,160]; (2) When atypical pathogens are suspected, doxycycline or minocycline or respiratory quinolones are preferred. Macrolides can be used in regions with lower resistance rate to mycoplasma
Patients with underlying disease(s) or elderly patients (age ≥ 65 years)	*S. pneumoniae*, *H. influenzae*, *Enterobacteriaceae* such as *K. pneumoniae*, influenza virus, RSV, *M. catarrhalis*, anaerobic bacteria, *Legionella*	(1) Penicillins-β-lactamase-inhibitor combinations; (2) III generation cephalosporins or their enzyme-inhibitor combinations, carbapenems such as cephamycins, oxacephems, ertapenem; (3) monotherapy of the above drugs or in combination with macrolides; (4) respiratory quinolones	(1) *Enterobacteriaceae* infection must be considered in patients with underlying disease(s) and elderly patients. The patients must be further evaluated for the risk of infection with ESBLs-producing *Enterobacteriaceae*; (2) Elderly patients should be monitored for the risk factors of aspiration
Requirement for ICU admission (Intravenous administration is recommended)			
Young adults without underlying disease(s)	*S. pneumoniae*, *S. aureus*, influenza virus, adenovirus, *Legionella*	(1) Penicillins-β-lactamase-inhibitor combinations, III generation cephalosporins, cephamycins, oxacephems, ertapenem combined with macrolides; (2) respiratory quinolones	(1) *S. pneumoniae* is the most common pathogen. The other pathogens such as *S. aureus*, *Legionella*, influenza virus should also be considered [1,2,161–165]; (2) During influenza seasons, attention must be paid

(Continues)

TABLE 6 (Continued)

Populations	Common pathogens	Anti-infective agents for initial empirical therapy	Comment
			to influenza viral infections. Combination with neuraminidase inhibitors should be considered. Attention should be paid to secondary *S. aureus* infection.[166] The agents active against MRSA can be used in combination if necessary
Patients with underlying disease(s) or elderly patients (age ≥ 65 years)	*S. pneumoniae*, *Legionella*, *Enterobacteriaceae* such as *K. pneumoniae*, *S. aureus*, anaerobic bacteria, influenza virus, RSV	(1) Penicillins-β-lactamase-inhibitor combinations, III generation cephalosporins or in combination with beta-lactamase inhibitors, carbapenems such as ertapenem combined with macrolides; (2) penicillins-β-lactamase-inhibitor combinations, III generation cephalosporins or in combination with beta-lactamase inhibitors, carbapenems such as ertapenem combined with respiratory quinolones	(1) Evaluate the risk of infection with ESBLs-producing *Enterobacteriaceae*; (2) Physicians should be aware of the risk factors for aspiration and antimicrobial coverage of relevant pathogens
CAP with risk factors for *P. aeruginosa* infection and requirement for inpatient treatment or ICU admission (Intravenous administration is recommended)			
Patients with structural lung disease	*P. aeruginosa*, *S. pneumoniae*, *Legionella*, *Enterobacteriaceae* such as *K. pneumoniae*, *S. aureus*, anaerobic bacteria, influenza virus, RSV virus	(1) β-lactams with antipseudomonal activity; (2) quinolones with antipseudomonal activity; (3) β-lactams with antipseudomonal activity combined with quinolones or aminoglycosides with antipseudomonal activity; (4) combination of β-lactams, aminoglycosides and quinolones with antipseudomonal activity	Risk factors include: (1) airway *P. aeruginosa* colonization; (2) repeated doses of antibacterial drugs or glucocorticoids due to chronic airway disease. Combination therapy is recommended for patients with severe CAP or proven antimicrobial resistance

I generation cephalosporins: cefazolin, cefradine, cephalexin, cefathiamidine and so on. II generation cephalosporins: cefuroxime, cefamandole, cefotiam, cefaclor, cefprozil, and so on. III generation cephalosporins: intravenous: ceftriaxone, cefotaxime, ceftizoxime and so on; oral: cefdinir, cefixime, cefpodoxime proxetil, cefditoren pivoxil and so on. Respiratory quinolones: levofloxacin, moxifloxacin, gemifloxacin. Aminopenicillins: amoxicillin, ampicillin. Penicillins-β-lactamase-inhibitor combinations (not including penicillins with antipseudomonal activity, such as piperacillin, ticarcillin): amoxicillin-clavulanic acid, amoxicillin-sulbactam, ampicillin-sulbactam and so on. Macrolides: azithromycin, clarithromycin, erythromycin. Quinolones with antipseudomonal activity: ciprofloxacin, levofloxacin. Beta-lactams with antipseudomonal activity: ceftazidime, cefepime, aztreonam, piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin-clavulanic acid, cefoperazone, cefoperazone-sulbactam, imipenem-cilastatin, meropenem, panipenem-betamipron, biapenem. Cephamycins: cefoxitin, cefmetazole, cefotetan, cefminox. Oxacephems: moxalactam, flomoxef. Aminoglycosides: amikacin, gentamicin, etimicin, netilmicin, tobramycin and so on. Neuraminidase inhibitors: oseltamivir, zanamivir, peramivir. Drugs for treating MRSA pneumonia: vancomycin, linezolid, teicoplanin, norvancomycin, ceftaroline.

ESBL: extended spectrum β-lactamase; MRSA: methicillin-resistant *Staphylococcus aureus*; RSV: respiratory syncytial virus.

TABLE 7 Common pathogens of CAP, common anti-infective agents, as well as dosage and administration

Pathogens	Preferred anti-infective agents	Alternate anti-infective agents	Comment
Streptococcus pneumoniae			
Penicillin MIC < 2 mg/L	Penicillin G 1.6–2.4 million units, IV q4h-q6h; ampicillin 4–8 g IV, divided into 2–4 doses; ampicillin-sulbactam 1.5–3 g IV q6h; amoxicillin-clavulanic acid 1.2 g IV q8h-q12h; cefazolin 0.5–1 g IV q6h-q8h; cefradine 0.5–1 g IV q6h; cefuroxime 0.75–1.5 g IVq8h; moxalactam 1–2 g IV q8h; cephamycins[a]	Ceftriaxone; cefotaxime; clindamycin; doxycycline; quinolones[b]; azithromycin; clarithromycin	
Penicillin MIC ≥ 2 mg/L	Cefotaxime 1–2 g IV q6h-q8h; ceftriaxone 1–2 g IV q24h; levofloxacin 0.5–0.75 g IV once daily; moxifloxacin 0.4 g IV once daily; gemifloxacin 0.32 g oral, once daily	High-dose ampicillin (2 g IV q6h); vancomycin; norvancomycin; linezolid; ceftaroline	
Haemophilus influenzae			
Non-β-lactamase-producing	Ampicillin 4–8 g/d IV, divided into 2–4 doses; ampicillin-sulbactam 1.5–3 g IV q6h; amoxicillin-clavulanic acid 1.2 g IV q8h-q12h; cefuroxime 0.75–1.5 g IV q8h; moxalactam 1–2 g IV q8h; cephamycins[a]	Quinolones[b]; doxycycline; azithromycin; clarithromycin; ceftriaxone; cefotaxime; TMP-SMX	
β-lactamase-producing	Amoxicillin-clavulanic acid 1.2 g IV q6h or q8h; ampicillin-sulbactam 1.5–3 g IV q6h; cefuroxime 0.75–1.5 g IV q8h; cefotaxime 1–2 g IV q6h-q8h; ceftriaxone 1–2 g IV q24h	Quinolones[b]; azithromycin; aminoglycosides[c]	25%-35% of strains are β-lactamase positive, and highly resistant to TMP-SMX and doxycycline.
Moraxella catarrhalis	Amoxicillin-clavulanic acid 1.2 g IV q8h-q12h; ampicillin-sulbactam 1.5–3 g IV q6h; cefuroxime 0.75–1.5 g IV q8h; cephamycins[a]; moxalactam 1–2 g IV q8h	Ceftriaxone; cefotaxime; quinolones[b]; azithromycin; clarithromycin; doxycycline; minocycline; TMP-SMX	
Staphylococcus aureus			
Methicillin-susceptible	Oxacillin 1–2 g IV q4h; cloxacillin 2–4 g/d IV, divided into 2–4 doses; ampicillin 4–8 g/d IV, divided into 2–4 doses; amoxicillin-clavulanic acid 1.2 g IV q8h-q12h; ampicillin-sulbactam 1.5–3 g IV q6h; cefazolin 0.5–1 g IV q6h-q8h; cefradine 1–2 g IV q6h or q8h; cefuroxime 0.75–1.5 g IV q8h; moxalactam 1–2 g IV q8h; cephamycins[a]	Clindamycin; azithromycin; erythromycin; clarithromycin; doxycycline; minocycline; cefotaxime; ceftriaxone; cefepime; levofloxacin; gemifloxacin; moxifloxacin	The target trough blood concentration of vancomycin is 15–20 mg/L. Some authors recommend a loading dose of 25–30 mg/kg. Two randomized trials showed that the efficacy of linezolid was equivalent to that of vancomycin, and subgroup analysis showed that MRSA patients who showed improvement had a higher survival rate in linezolid group compared with vancomycin group. Vancomycin and linezolid should not be used together due to antagonistic effect.

(Continues)

TABLE 7 (Continued)

Pathogens	Preferred anti-infective agents	Alternate anti-infective agents	Comment
Methicillin-resistant	Vancomycin 1 g IV q12h or 0.5 g q6h; linezolid 600 mg IV q12h	Norvancomycin; teicoplanin; ceftaroline; tigecycline; rifampin; fosfomycin; TMP-SMX (used in combination, not suitable for monotherapy)	If MIC of vancomycin is $\geq$ 2 mg/L, an alternative regimen should be used.
Pseudomonas aeruginosa	β-lactams with anti-*Pseudomonas aeruginosa* effect[c] ± ciprofloxacin 400 mg IV q8h-q12h or ± levofloxacin 750 mg IV once daily or aminoglycosides[c]	Aminoglycosides[d] + ciprofloxacin or levofloxacin. In case of multiple-drug resistance, polymyxin should be used	When aminoglycosides are combined with cyclosporin, vancomycin, amphotericin B, or radiographic contrast agent, the risk for renal toxicology increases. Such combined therapy are applicable for patients with severe CAP, but the therapeutic value is controversial
Klebsiella pneumoniae* and *Enterobacteriaceae			
Non-β-lactamase-producing	Cefuroxime 0.75–1.5 g IV q8h; cefotaxime1–2 g IV q6h-q8h; ceftriaxone1–2 g IV q24h; β-lactams-β-lactamase inhibitor combinations[e]; cephamycins[a]	Cefepime; levofloxacin; moxifloxacin; gemifloxacin; aminoglycosides[d]	ESBLs can inactivate all cephalosporins. It is difficult to predict the activity of β-lactams-β-lactamase combinations. ESBLs-producing strains are also resistant to all quinolones and most aminoglycosides.
ESBLs-producing *Enterobacteriaceae*	Carbapenems[f], piperacillin-tazobactam 4.5 g IV q6h-q8h; cefoperazone-sulbactam 2–4 g IV q8h-q12h	Cefepime; tigecycline	Fourth-generation cephalosporins and piperacillin-tazobactam have *in-vitro* antibacterial activity, but their efficacy has not yet been completely demonstrated in animal models.
***Enterobacteriaceae* with high production of AmpC β-lactamase**	Carbapenems[f]	Cefepime; tigecycline	Quinolones can be effective against susceptible strains, but most strains are resistant. Some bacterial strains are susceptible to injectable II and III generation cephalosporins in vitro, but are resistant to ceftazidime.
Carbapenemase-producing *Enterobacteriaceae*	Polymyxin B 15 000–25 000 U/kg per day, IV, in 2 separate doses	Tigecycline; drugs to which pathogens are relatively susceptible could be selected for combination therapy	Patients infected with these bacterial strains are unresponsive to injectable II or III generation cephalosporins. Tigecycline has in vitro activity.
Acinetobacter	Ampicillin-sulbactam 3 g IV q6h; cefoperazone-sulbactam 2–4 g IV q12h or q8h; quinolones[b] + amikacin 15 mg/kg IV q24h or + ceftazidime 2 g IV q8h-q12h; carbapenems[f]	Cefoperazone-sulbactam + amikacin or minocycline; polymyxin B; polymyxin E; tigecycline; sulbactam[g] + minocycline or polymyxin E or amikacin or carbapenem[f]	The sulbactam component in ampicillin-sulbactam has antibacterial activity with an appropriate dosage of 3 g IV q6h, and has been reported to be superior to polymyxin E *A. baumannii* in China is highly resistant to carbapenems, which is normally used at MIC $\leq$ 8 mg/L. Combination therapy is recommended.

(Continues)

TABLE 7 (Continued)

Pathogens	Preferred anti-infective agents	Alternate anti-infective agents	Comment
Anaerobic bacteria	Penicillins-β-lactamase-inhibitor combinations[e]	Clindamycin; metronidazole; doxycycline; moxifloxacin; carbapenems[f]	
Mycoplasma pneumoniae	Doxycycline first dose 200 mg oral, followed by 100 mg oral, twice daily; minocycline 100 mg oral, twice daily; levofloxacin 500 mg IV or oral, once daily; moxifloxacin 400 mg IV or oral, once daily	Azithromycin; clarithromycin; gemifloxacin	The application of macrolides should be based on local susceptibility data. Clindamycin and β-lactams are ineffective on *M. pneumoniae*.
Chlamydia pneumoniae	Azithromycin 500 mg IV once daily; clarithromycin 500 mg oral, twice daily; erythromycin 500 mg IV q6h; levofloxacin 500 mg IV or oral, once daily; moxifloxacin 400 mg IV or oral, once daily	Doxycycline; minocycline; gemifloxacin	
Legionella	Azithromycin 500 mg IV once daily or erythromycin 0.5 g IV q6h; levofloxacin 500 mg IV or oral, once daily; gemifloxacin 0.32 g oral, once daily; moxifloxacin 400 mg IV or oral, once daily	Doxycycline; clarithromycin; minocycline; TMP-SMX; above-mentioned quinolones + rifampin or azithromycin	When quinolones are combined with macrolides, the potential risk of abnormalities in cardiac electrophysiology should be alerted.
Chlamydia psittaci	Doxycycline 100 mg IV or oral, twice daily; minocycline100 mg oral, twice daily	Azithromycin; clarithromycin; erythromycin; chloramphenicol	Fever and other symptoms can normally be controlled within 48–72 h, but antibiotics should be continued for at least 10 d.
Coxiella burnetii	Doxycycline 200 mg oral, once daily; minocycline 100 mg oral, twice daily	Erythromycin; chloramphenicol; levofloxacin; moxifloxacin; gemifloxacin	Q fever
Burkholderia pseudomallei	Ceftazidime 30–50 mg/kg IVq8h; imipenem 20 mg/kg IV q8h. Treatment continued for at least 10 d. If the condition is improved, therapy may be switched to oral treatment.	Intravenous therapy followed by oral treatment: chloramphenicol 10 mg/kg q6h × 8 weeks; doxycycline 2 mg/kg twice daily × 20 weeks; TMP-SMX 5 mg (based on TMP) twice daily × 20 weeks Quinolones[b]	Pregnant women: oral amoxicillin-clavulanic acid sustained-release tablets 1000/62.5 mg, 2 tabs twice daily × 20 weeks. Even with very good compliance, relapse rate is still 10%. The maximum daily dose of ceftazidime is 6 g. Tigecycline: susceptible in vitro, but no clinical data. 12%-80% of bacterial strains are resistant to TMP-SMX in Thailand. Quinolones are effective in vitro. Doxycycline + chloramphenicol + TMP-SMX has better sustained efficacy compared with doxycycline monotherapy. Meropenem is also effective
Bordetella pertussis	Azithromycin 0.5 g IV once daily; erythromycin 0.5 g IV q6h	TMP-SMX; clarithromycin	
Stenotrophomonas maltophilia	TMP-SMX 0.48 g (80 mg + 400 mg dosage form) oral, 2–3 tablets, tid; ticarcillin-clavulanic acid 3.2 g IV q6h-q8h	Cefoperazone-sulbactam; piperacillin-tazobactam; ceftazidime; moxifloxacin; ticarcillin-clavulanic acid + aztreonam	Ticarcillin-clavulanic acid + TMP-SMX; ticarcillin-clavulanic acid + ciprofloxacin have synergetic antibacterial effect in vitro.

(Continues)

TABLE 7 (Continued)

Pathogens	Preferred anti-infective agents	Alternate anti-infective agents	Comment
Nocardia	TMP-SMX 15 mg/kg daily (based on TMP) oral, divided into 2–4 doses, for 3–4 weeks, followed by 60 mg/kg daily, oral, divided into 2–4 doses, for 3–4 months	Imipenem-cilastatin + amikacin 7.5 mg/kg IV q12h, × 3–4 weeks; followed by TMP-SMX for 3–4 months	The duration of therapy is 3–4 months for primary pulmonary nocardiosis.
Actinomycetes	Ampicillin 2 g IV q8h, for 4–6 weeks, followed by penicillin V potassium 2–4 g/kg per day, oral, for 3–6 weeks	Piperacillin; amoxicillin-clavulanic acid; ampicillin-sulbactam; piperacillin-tazobactam; doxycycline; minocycline; ceftriaxone; clindamycin; chloramphenicol; azithromycin; erythromycin; moxifloxacin; imipenem; ertapenem	Penicillin G is an alternative to ampicillin: 10–20 million U/d, IV, divided into 4–6 separate doses, for 4–6 weeks.
Yersinia pestis	Gentamicin 5 mg/kg IV once daily	Doxycycline; minocycline	TMP-SMX can be used to prevent *Yersinia pestis* pneumonia. Chloramphenicol is effective but with high toxicity. Cephalosporins and quinolones are effective in animal models.
Anthrax pneumonia	Ciprofloxacin 400 mg IV q12h or levofloxacin 500 mg IV once daily or doxycycline 100 mg IV q12h + clindamycin 900 mg IV q8h ± rifampin 300 mg IV q12h; Switch to oral therapy and reduce dosage after improvement: ciprofloxacin 500 mg oral, twice daily; clindamycin 450 mg oral, q8h, and rifampin 300 mg oral, twice daily. Duration of therapy is 60 d.	Penicillin G	Clindamycin can inhibit the production of toxins. Rifampin can enter cerebrospinal fluid and into cells. If the isolated pathogen is susceptible to penicillin, penicillin 4 million U IV q4h should be given. If structural or inductive β-lactamase is produced, penicillin or ampicillin should not be used alone. Cephalosporins or TMP-SMX should not be used. Erythromycin and azithromycin have borderline activity. Clarithromycin is effective. Moxifloxacin is effective, but without clinical data.
Influenza virus or human infections with avian influenza virus	Oseltamivir 75 mg oral, twice daily × 5 d, for obesity patients, the dosage is increased to 150 mg oral, twice daily; for patients with severe influenza, increased dosage (150 mg twice daily) and prolonged course of treatment (eg, ≥ 10 d) should be considered. The safety of high dose therapy for pregnant women has not been established. Zanamivir 2 sprays (5 mg/spray) twice daily × 5 d	Amantadine; rimantadine Peramivir 600 mg IV once daily for at least 5 d can be considered for patients with severe life-threatening conditions	For patients with chronic obstructive pulmonary disease or asthma, zanamivir can potentially cause bronchospasm. Most epidemic viral strains are resistant to amantadine and rimantadine.
Adenovirus	Cidofovir 1 mg/kg IV once daily × 2 weeks, and oral probenecid 2 g should be given every time before injection. And 1 g oral probenecid should		The drug is contraindicated when serum creatinine >1.5 mg/dL, CrCl ≤ 55 mL/min, or urine protein ≥ 100 mg/L.

(Continues)

TABLE 7 (Continued)

Pathogens	Preferred anti-infective agents	Alternate anti-infective agents	Comment
	be taken at 2 h and 8 h post-infusion. Renal functions should be monitored.		
Respiratory syncytial virus	No specific drug so far	Ribavirin 0.5–1 g/d IV q12h (not recommended for regular use)	Therapies are mainly symptomatic treatments, including fluid replacement and oxygen therapy.
Middle East respiratory syndrome coronavirus	No specific drug so far	Pegylated interferon α-2a subcutaneous, 180 μg weekly × 2 weeks + ribavirin first dose 2000 mg po, followed by 1200 mg oral, q8h × 4 d, then 600 mg oral, q8h × 4–6 d (the dose of ribavirin should be adjusted based on liver functions, and kidney functions should be monitored)[167]	Retrospective studies showed that the therapy could increase 14-day survival in patients with severe conditions, but 28-day survival was not be increased. It may cause decrease of hemoglobin level.
Aspergillus	Voriconazole 6 mg/kg IV q12h on the first day, followed by 4 mg/kg IV q12h or 200 mg oral, q12h (body weight ≥ 40 kg), or 100 mg oral, q12h (body weight < 40 kg); amphotericin B liposome 3–5mg/kg daily IV, or amphotericin B liposome compound 5 mg/kg daily IV, or amphotericin B 0.75–1 mg/kg daily IV (initial dose 1–5 mg/d)	Itraconazole; caspofungin; micafungin; posaconazole	Voriconazole has better efficacy than amphotericin B. For patients with CrCl < 50 mL/min, the drug should only be taken orally. IV administration is contraindicated. The efficacy rate of caspofungin is about 50% for invasive pulmonary aspergillosis. It can be used as a rescue therapy. The role of combination therapy is unclear, it is not regularly recommended, but can be considered for refractory cases. The classic combination treatment is echinocandins combined with amphotericin B liposome.
Mucor	Amphotericin B liposome 3–5 mg/kg daily IV or amphotericin B liposome compound 5 mg/kg daily IV or amphotericin B 0.75–1 mg/kg daily IV (initial dose 1–5 mg/d)	Posaconazole	The complete or partial response rate of posaconazole rescue regimen is 60%-80%.
Human pneumocystis pneumonia			
Non-acute patients who can take the drug orally and PaO_2 > 70 mm Hg	TMP-SMX (160/800 mg dosage from) 2 tabs oral, q8h × 21 d or dapsone 100 mg oral, once daily + TMP 5 mg/kg oral, tid × 21 d	Clindamycin 300–450 mg oral, q6h + primaquine base 15 mg oral, once daily, for 21 d, or atovaquone suspension 750 mg oral, twice daily, at meal time × 21 d	Patients with severe life-threatening conditions can take glucocorticoids: start with prednisone 40 mg oral, twice daily × 5 d, followed by 40 mg oral, once daily × 5 d, then 20 mg oral, once daily × 11 d.

(Continues)

TABLE 7 (Continued)

Pathogens	Preferred anti-infective agents	Alternate anti-infective agents	Comment
Acute patients who cannot take the drug orally and PaO_2 < 70 mm Hg (dry cough, progressive dyspnea, diffuse pulmonary infiltrates)	Glucocorticoids should be given 15–30 min before TMP-SMX which should be administered in a dosage of 15 mg/kg/d divided into separate doses once per 8 h (calculated based on TMP content) or 2 tabs once per 8 h, continued for 21 d	Clindamycin 600 mg IV q8h + primaquine base 30 mg oral, once daily; pentamidine isethionate 4 mg/kg daily IV for 21 d	Although TMP-SMX-resistant *Pneumocystis* is rarely observed, but it does exist. Caspofungin is effective in animal models.

The selection of antimicrobial agents should ultimately depend on susceptibility testing results and the opinions of local microbiological specialists. The appropriate dosage of antimicrobial agents should be based on local data. CrCl, creatinine clearance; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Cefoxitin 1–2 g IV q8h-q6h; cefmetazole 1–2 g q8h-q12h; cefotetan 1–3 g IV q12h (maximum dose ≤ 6 g once daily); cefminox 1 g IV q8h.

[b] Levofloxacin, moxifloxacin, gemifloxacin (not as first-line therapy for penicillin-susceptible strains); ciprofloxacin is mainly used in treatment of gram-negative bacteria (including *H. influenzae*).

[c] Ticarcillin 3 g IV q4h-q6h; piperacillin 2–4 g IV q4h-q6h; piperacillin-tazobactam 4.5 g IV q6h-q8h; aztreonam 1–2 g IV q8h-q12h; ceftazidime 1–2 g IV q8h-q12h; cefepime 1–2 g IV q8h-q12h; cefoperazone 1–2 g IV q8h; cefoperazone-sulbactam (2:1) 3 g q8h-q12h; imipenem-cilastatin (for *P. aeruginosa*) 500 mg (based on imipenem) IV q6h-q8h; meropenem 1–2 g IV q8h; panipenem-betamipron 1–2 g IV q8h-q12h; biapenem 0.3 g IV q12h.

[d] Gentamicin or tobramycin 5.1 mg/kg daily IV, once daily; amikacin 15 mg/kg IV once daily; etimicin 0.2–0.3 g IV once daily; netilmicin 6.5 mg/kg IV, once daily.

[e] Piperacillin-tazobactam 4.5 g IV q6h-q8h; ticarcillin-clavulanic acid 3.2 g IV q6h-q8h; ampicillin-sulbactam 1.5–3 g IV q6h or amoxicillin-clavulanic acid 1.2 g IV q8h-q12h.

[f] Imipenem-cilastatin 500 mg (based on imipenem) IV q6h-q8h; meropenem 1–2 g IV q8h; ertapenem 1–2 g IV q24h; panipenem-betamipron 1–2 g IV q8h-q12h; biapenem 0.3 g IV q12h.

[g] Sulbactam: 4–8 g/d IV, divided into 2–4 doses.

therapy and assisted ventilation are also important to improve the outcomes of patients. Additionally, nebulization, postural drainage and chest physical therapy are also used in CAP treatment[169–171] (II B). Adjunctive drugs for severe CAP also include glucocorticoids, intravenous immune globulin and statins, although currently there is no conclusive evidence for their effectiveness[172] (II B).

7.1 | Oxygen therapy and assisted respiration

1. The blood oxygen level of hospitalized CAP patients should be evaluated in a timely manner. Oxygen therapy via nasal catheter or face mask is recommended for patients with hypoxemia in order to maintain blood oxygen saturation at above 90%. Additionally, for patients with risk of hypercapnia, oxygen saturation should be maintained at 88%-92% before obtaining the results of blood gas analysis[173,174] (III A). The results of recent studies showed that heated and humidified high-flow oxygen therapy via nasal catheter (40–60 L/min) could also be used in clinical practice[175,176] (II B).
2. Compared with high-concentration oxygen therapy, noninvasive ventilation (NIV, including bilevel positive airway pressure or continuous positive pressure ventilation) can decrease the endotracheal intubation rate and mortality of CAP patients with acute respiratory failure,[177–181] improve oxygenation index faster and more significantly,[177,178,182,183] and decrease the incidence of multiple organ failure,[179] and septic shock.[177] These benefits are more significant for patients with concomitant chronic obstructive pulmonary disease[180] (II B). However, for CAP patients with acute respiratory distress syndrome (ARDS), NIV has shown high failure rate[184] and it cannot improve prognosis.[177] NIV is also not appropriate for CAP patients with severe hypoxemia (oxygenation index < 150 mm Hg)[184] (II A).
   Additionally, the failure of NIV must be recognized timely. NIV failure is indicated if NIV cannot improve respiratory rate or oxygenation state within the initial 1–2 h,[180,184,185] or the therapy cannot decrease the blood carbon dioxide level in a patient with initial hypercapnia.[180] The oxygen therapy should be switched to tracheal intubation and ventilator-assisted ventilation immediately (II A).
3. Mechanical ventilation with low tidal volume (6 mL/kg ideal body weight) should be used for CAP patients with ARDS after tracheal intubation[186,187] (I A).
4. For patients with severe CAP and concomitant ARDS, extracorporeal membrane oxygenation (ECMO) can be used if regular mechanical ventilation cannot lead to improvement[188–191] (II B). Indications of ECMO include: (1) reversible respiratory failure associated with severe

hypoxemia (oxygenation index < 80 mm Hg or hypoxemia that cannot be corrected even after 6 h high-level positive end-expiratory pressure [PEEP] assisted-ventilation); (2) serious decompensatory acidosis (pH < 7.15); (3) excessively high plateau pressure (eg, > 35–45 cm H_2O).[192]

7.2 | Glucocorticoids

Glucocorticoids can decrease the mortality of CAP patients complicated with septic shock.[193–195] Hydrocortisone succinate 200 mg/day is suggested based on the treatment of septic shock.[196] The drug should be stopped promptly after septic shock is corrected. The duration of therapy is normally no more than 7 days (II C). The benefits of glucocorticoids are unclear for other severe CAP patients without septic shock. Additionally, systemic use of glucocorticoids can cause insulin-requiring hyperglycemia.[197,198]

8 | SECTION 6. ASSESSMENT AFTER INITIAL THERAPY AND THE CRITERIA FOR DISCHARGE

For most CAP patients, clinical symptoms can be improved 72 h after the initial therapy, while radiographic improvement lags behind clinical symptoms.[199–202] Disease status should be assessed 72 h after initial therapy. Some patients are slower to respond to therapies. In such cases, it is appropriate to continue the therapy without a need to change the regimen immediately as long as no exacerbation occurs in clinical manifestations[1,203–205] (I A).

8.1 | Assessment after initial therapy

The initial therapy is assessed as effective or failure based on the patient's response to treatment, and subsequent management is provided accordingly. Assessment after initial therapy should include the following 5 aspects:

1. *Clinical manifestations*: including respiratory and systemic symptoms and signs (III A).
2. *Vital signs*: general condition, consciousness, body temperature, respiratory rate, heart rate, blood pressure and so on.[2] (I A).
3. *General laboratory tests*: including routine blood test, blood biochemistry, blood gas analysis, C-reactive protein, procalcitonin and so on. It is recommended to repeat C-reactive protein, procalcitonin and routine blood tests after 72 h for hospitalized patients in order to differentiate between treatment failure and slow response to therapy. Patients with severe conditions should be monitored closely[2,206–209] (II B).
4. *Microbiological tests*: it is appropriate to repeat regular microbiological tests. Molecular biological and serological assays can be used when necessary. Efforts should be made to obtain etiological evidence[210–220] (II B).
5. *Chest radiography*: it is not recommended to repeat chest radiography regularly for patients with significant improvement in clinical symptoms. When symptoms and signs persist or exacerbate, chest X-ray or chest CT should be repeated to identify the changes of lung lesions[2] (I A).

8.2 | Definition of effective initial therapy and subsequent management

1. An effective initial therapy is defined as the situation that the clinical condition of a patient is stabilized after therapy. All the 5 criteria below must be met for clinical stability: (1) body temperature ≤ 37.8°C; (2) heart rate ≤ 100 bpm; (3) respiratory rate ≤ 24 bpm; (4) systemic blood pressure ≥ 90 mm Hg; (5) O_2 saturation ≥ 90% (or arterial partial pressure of O_2 ≥ 60 mm Hg, while breathing air)[1,221] (II A).
2. Subsequent management is recommended after an effective initial therapy: (1) For patients with significant improvement in symptoms after initial therapy, it is appropriate to continue the same anti-infective treatment (I A). (2) For patients who have achieved clinical stability and are able to receive oral therapy, sequential therapy should be administered with pathogen-susceptible oral preparations of the same types of antimicrobial agents or another agent with similar antibacterial spectrum[1,222] (I A).

8.3 | Definition of failed initial therapy and subsequent management

1. A failed initial therapy is defined as either of the following situations in a patient: the symptoms are not improved after initial therapy, and requiring alternative antibiotics; exacerbation and disease progression after initial improvement during initial therapy (II A).
   Two forms of failure are primarily observed in clinical practice[223,224]: (1) Progressive pneumonia: disease progresses to acute respiratory failure requiring mechanical ventilation support or septic shock requiring vasoactive drug therapy within 72 h from arrival at the hospital[223,224]; (2) Unresponsive to therapies[221,225]: patient cannot achieve clinical stability 72 h after initial therapy.
2. Local or systemic complications,[2,205,226] such as parapneumonic effusion, empyema, ARDS, phlebitis, septicemia and metastatic abscesses, are risk factors for failure of initial therapy. Other potential factors include nonbacterial infection or antibiotic-resistant bacterial infection not

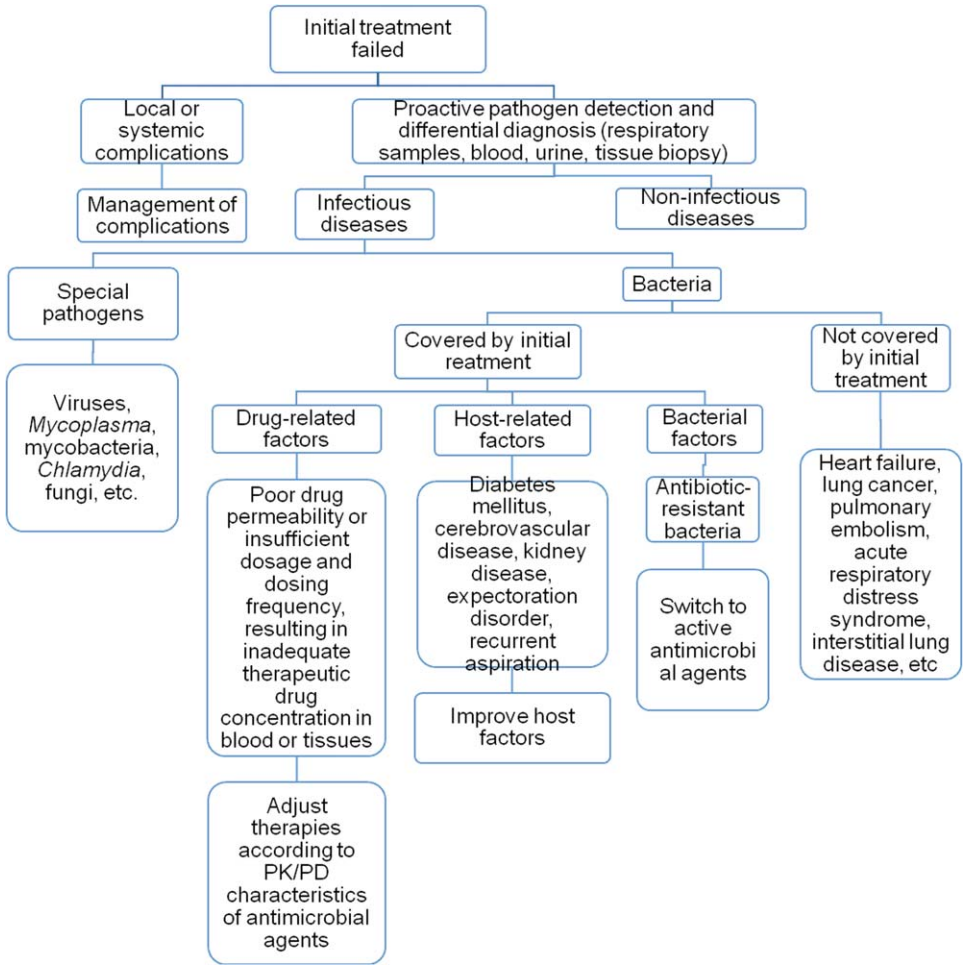

FIGURE 1 Flowchart for failure of initial treatment

covered by initial treatment, and noninfectious diseases. See the flowchart for failure of initial treatment (Figure 1) for details.[1,17,18,51,223,226,227]

8.4 | Criteria for hospital discharge

Discharge can be considered when a patient with clear diagnosis shows significant improvement after effective treatment, evidenced by normal body temperature for more than 24 h, and the other 4 criteria for clinical stability are satisfied. Moreover, the patient is able to receive oral treatment, and there is no other complications or disturbance of consciousness requiring further management[1] (I A).

9 | SECTION 7. UNUSUAL TYPES OF CAP

9.1 | Unusual pathogens

9.1.1 | Viral pneumonia

Respiratory tract viruses play an important role in adult CAP. They can be direct responsible pathogens for CAP, or facilitate the onset of secondary bacterial pneumonia due to *S. pneumoniae*, *S. aureus*, and so on. Both primary viral pneumonia and secondary or concomitant bacterial infections can be severe.[53,228] Viruses are reported to be detected in 15%-34.9% of Chinese adult CAP patients with normal immune status.[15,26,27] Common viruses in adult CAP include influenza virus, parainfluenza virus, rhinovirus, adenovirus, hMPV and RSV. Since 2009, the new H1N1 influenza A virus has become a major viral strain for seasonal influenza, along with seasonal viral strain H3N2.[15,26,27,229–234] In recent years, there have also been cases of pneumonia caused by avian influenza A virus (H5N1, H7N9 and H10N8) and imported Middle East respiratory syndrome (MERS) coronavirus.[235–252] Early diagnosis based on epidemiological (such as epidemic season and history of traveling to epidemic regions) and clinical characteristics, early antiviral therapy (within 48 h of the onset of the disease), and reasonable supportive therapies are critical measures to reduce mortality[101,229,230,253–255] (II B). See Table 8 for the epidemiological and clinical characteristics and treatment of viral pneumonia. See corresponding sections of this guideline for information on diagnosis and prophylaxis. Epidemiological clues are especially important in patients with highly contagious and newly discovered respiratory tract viruses.

TABLE 8 Epidemiological and clinical characteristics and treatment of pneumonia caused by major respiratory tract viruses

Respiratory tract virus	Key epidemiological features	Clinical characteristics	Radiographic characteristics	Antiviral treatment
H1N1 influenza A virus, H3N2 influenza virus	The epidemic season in the north is from November to the end of February of next year, and in the south – another peak season is from May to August. Influenza outbreak can occur in any season. High-risk populations include the elderly (age $\geq$ 65 years), patients with underlying diseases, obesity, or immunosuppression and second- to third-trimester pregnant women.[101] The virus can be transmitted *via* air, saliva droplets and direct contact. The incubation period is normally 1–7 d, and most commonly 2–4 d.	Fever, cough, normal or decreased WBC, normal or decreased lymphocytes, CRP < 20 mg/L, creatine kinase or lactate dehydrogenase can increase. The disease can progress rapidly in some patients, causing persistent high fever, severe dyspnea and intractable hypoxemia.[229–234]	For patients with severe conditions, ground-glass opacities or patchy nodule infiltrates can appear in bilateral lungs, which may be associated with consolidation	Oseltamivir, zanamivir, peramivir[101,229,254,256–258] (I A)
Human infections with avian influenza virus	Human beings lack immunity against avian influenza virus. Individuals in close contact with domestic animals dying from unknown reasons, livestock markets, or patients with confirmed diagnosis of avian influenza constitute the high exposure population.[241,255] The virus is primarily transmitted through contact with dead animals with avian influenza and the contaminated objects and environment. There is a small number of cases of person-to-person transmission of H5N1. The incubation period is normally no more than 7 d.	Similar to pneumonia caused by influenza virus, but decreased WBC, lymphocyte count and platelet count are more common and there is a more significant increase in alanine transaminase, lactate dehydrogenase, and/or creatine kinase. Hemoptysis and abnormal coagulation functions are more commonly seen among patients infected with H7N9.[235,239,242,247–250]	Similar to pneumonia caused by influenza virus[235,239]	Same as pneumonia caused by influenza virus[255] (I A)
Adenovirus	The epidemic season is from February to May. The virus is commonly seen in adults without underlying disease.[26] The incubation period is 3–8 d. HAdV-55, HAdV-11 and HAdV-7 are relatively common serotypes[259,260]	Similar to pneumonia caused by influenza virus; more common in immunocompetent adults[259–262]	Patients with severe conditions primarily show pulmonary consolidation, which may be associated with ground-glass opacities or patchy nodule infiltrates in unilateral or bilateral lungs or multiple lobes [259,260,262]	Cidofovir [53,263] (II B)
Respiratory syncytial virus	RSV is an important pathogen of lower respiratory tract infections in infants and young children. In adults, infections are more common in the elderly or individuals with underlying cardiac or pulmonary diseases or immunosuppression[53,264,265]. The incubation period is 4–5 d.	Similar to pneumonia caused by influenza virus [53]	Characteristic manifestations are nodule opacities or tree-in-bud sign associated with bronchial wall thickening[266]	Intravenous or oral ribavirin (not recommended for routine use)[53,264,265,267] (II B)

(Continues)

TABLE 8 (Continued)

Respiratory tract virus	Key epidemiological features	Clinical characteristics	Radiographic characteristics	Antiviral treatment
Middle East respiratory syndrome (MERS) coronavirus	The general population are generally vulnerable. Special attention should be paid to history of travel or business trip to epidemic regions such as Saudi Arabia, UAE and so on, or history of close contact with patients with confirmed diagnosis of MERS.[268,269] The incubation period is 2–14 d.	Fever, associated with chills and shivers, cough, shortness of breath, muscle soreness; gastrointestinal symptoms such as diarrhoea, nausea and vomiting and abdominal pain are relatively common. Decreased platelet count, decreased lymphocyte count and increased lactate dehydrogenase and creatinine may be observed in some patients [268,269]	Mainly pulmonary involvement in subpleural and basal segments of lungs; broad appearance of ground-glass opacities, which may be associated with consolidation. Pleural effusion, interlobular septal thickening may also appear [269,270]	Ribavirin combined with interferon [168,271] (II C)

9.1.2 | *Legionella* pneumonia

In China, *Legionella* pneumonia accounts for 5.08% of CAP.[17] *Legionella* pneumonia usually progresses to severe condition. Almost 50% of the hospitalized patients due to *Legionella* infections require ICU admission,[272] and the mortality is up to 5%-30%.[272] Susceptible populations include the elderly, males, smokers,[273,274] individuals with chronic underlying cardiac or pulmonary diseases,[272,274–276] diabetes mellitus,[274,275] malignant tumour, immunosuppression[273–275] and use of tumour necrosis factor-α antagonists.[277] The relevant epidemiological history includes contact with contaminated air conditioners, air conditioner cooling tower, or contaminated potable water, hot recreational spa, gardening activities or plumbing repairs and the history of traveling to an area with *Legionella* outbreak.[2,275,276,278]

The possibility of *Legionella* pneumonia should be suspected when an adult CAP patient develops the following conditions: fever but relative bradycardia, acute onset of headache, non-drug-induced disturbance of consciousness or sleepiness, non-drug-induced diarrhoea, acute renal and/or hepatic impairment, hyponatremia, hypophosphatemia and unresponsiveness to β-lactams.[164,276,278–283] The relatively specific manifestations of *Legionella* pneumonia in chest radiograph is sharply demarcated consolidation intermingled with ground-glass opacities. Another characteristic of *Legionella* pneumonia is radiographic progression within a short period of time (1 week) even though improvement in clinical symptoms. Or it may take several weeks or even months for pulmonary infiltrates to be completely absorbed.[284–286]

Macrolides, respiratory quinolones or doxycycline monotherapy are appropriate for immunocompetent patients with mild or moderate *Legionella* pneumonia. Quinolones combined with rifampin or macrolides are recommended for patients with severe conditions, or when monotherapy fails and those immunocompromised patient[1,2,287–290] (I A). When quinolones are combined with macrolides, physicians should pay close attention to the potential risk of abnormalities in cardiac electrophysiology[2] (I A).

9.1.3 | Community-acquired methicillin-resistant *S. aureus* pneumonia

Currently, CA-MRSA pneumonia is relatively rare in Mainland China. Only a small number of cases are reported in children and teenagers.[19–22] Similarly, among the skin and soft tissue infections caused by *S. aureus*, MRSA only accounts for a small proportion (5/164).[291] Among the pathogens of hospitalized CAP patients, the proportion of MRSA is 4.3% in Taiwan,[292] 3.3% in Japan[293] and 6.2%-8.9% in the United States according to a survey.[294] The estimated incidence of CA-MRSA pneumonia is 0.51–0.64/100 000

people.[295] CA-MRSA pneumonia is a severe disease associated with mortality up to 41.1%.[296] Vulnerable populations include patients or individuals with close contact with a MRSA carrier or patient, individuals affected by influenza virus, prisoners, professional athletes, individuals who serve in the army recently, men who have sex with men, intravenous drug users, regular sauna users and those using antibacterial agents before infection.[295]

CA-MRSA pneumonia progresses rapidly. The clinical symptoms include influenza-like symptoms,[296,297] fever, cough, chest pain, gastrointestinal symptoms and skin rashes. For patients with serious conditions, severe pneumonia symptoms such as hemoptysis, confusion, ARDS, multiple organ failure and shock may appear, as well as complications such as acidosis, disseminated intravascular coagulation, deep vein thrombosis, pneumothorax or empyema, pneumatocele, pulmonary abscess and acute necrotic pneumonia.[295] Radiographic characteristics of CA-MRSA pneumonia include extensive pulmonary consolidation and multiple cavities in bilateral lungs.[298] CA-MRSA pneumonia should be suspected after influenza or in previously healthy young patients in case of cavitation, necrotic pneumonia associated with rapid increase of pleural effusion, massive hemoptysis, neutropenia and/or erythematous rashes.[299] Glycopeptides or linezolid are the primary choice for CA-MRSA pneumonia[1,299] (III B).

9.2 | Special populations

9.2.1 | CAP in the elderly

Currently, the consensus definition of CAP in the elderly (elderly CAP) is pneumonia occurring in the population aged ≥ 65 years.[2,300,301] The incidence of elderly CAP increases with age.

The clinical manifestations of elderly CAP can be atypical.[302,303] The manifestations may only include poor appetite, urinary incontinence, tiredness and altered mental state and so on.[2,301] Typical manifestations of pneumonia such as fever, cough and increased WBC/neutrophil count may not be so evident.[303] Therefore, missed diagnosis and misdiagnosis may occur. Tachypnea is a sensitive index for diagnosis of elderly CAP.[304] When fever or any of the above-mentioned atypical symptoms appear, chest radiography should be done as early as possible to confirm the diagnosis.[304]

S. pneumoniae is still the main pathogen for elderly CAP, but the possibility of *Enterobacteriaceae* infection should be considered for elderly patients with underlying diseases (congestive heart failure, cardiovascular and cerebrovascular diseases, chronic respiratory system diseases, renal failure, diabetes mellitus, etc.).[24,300,305] These patients should be further evaluated for risk factors of ESBLs-producing *Enterobacteriaceae*. Empirical treatment with cephamycins, piperacillin-tazobactam, cefoperazone-sulbactam, ertapenem or other carbapenems is recommended for patients with high risk of infections with ESBLs-producing *Enterobacteriaceae*[145–147,306] (III B). Relevant risk factors include history of ESBLs-producing bacterial colonization or infection, prior use of third generation cephalosporins, history of repeated or long-term hospitalization, indwelling medical devices, renal replacement therapies.[142–144]

Elderly patients are associated with reduced organ functions, which must be monitored during treatment to avoid side effects. Reduced renal excretion may cause prolonged half-lives of drugs, so the dosage should be reasonably adjusted in terms of CrCl when treating such patients[304] (II B). If no contraindication exists, hospitalized elderly CAP patients should be evaluated for risk of deep vein thrombosis and prophylaxis with low molecular weight heparin should be administered when necessary[307] (II B).

The treatment failure rate is 6%-15% for elderly CAP.[308] Common reasons are concomitant severe sepsis, myocardial infarction, or progression of pneumonia.[309] Cardiovascular event is common in elderly CAP, which is one of the reasons for increased mortality.[308,309]

9.2.2 | Aspiration pneumonia

Aspiration pneumonia is pulmonary infectious lesions caused by aspiration of food, oropharyngeal secretion, or gastric content into the throat or lower respiratory tract, not including chemical inflammation in the lung due to aspiration of sterile gastric fluid.[310–312] The majority cases of aspiration pneumonia are caused by silent aspiration, accounting for around 71% of elderly CAP.[312]

The following points should be noted when making diagnosis of aspiration pneumonia: (1) whether there are risk factors for aspiration (eg, disturbance of consciousness due to cerebrovascular diseases or other reasons, dysphagia, periodontal diseases, or poor oral hygiene)[122,308,313–316]; (2) whether chest radiograph shows primary lesions in the posterior segment of upper lobe and dorsal or basal segment of the lower lobe, just as in hypostatic pneumonia.[312,317–319]

Aspiration pneumonia is mostly caused by infections with anaerobic bacteria, gram-negative bacteria or *S. aureus*. The treatment should cover the above pathogens and based on the severity of disease using antimicrobial agents with anti-anaerobic activity, such as amoxicillin-clavulanic acid, ampicillin-sulbactam, moxifloxacin, carbapenems or in combination with metronidazole or clindamycin[136,139–141,316,320,321] (II A). Targeted treatment can be administered after the results of sputum culture and antimicrobial susceptibility testing are available.

Intensive care is required for the elderly patients with risk factors of aspiration in order to reduce the incidence of aspiration pneumonia, specifically: (1) the head of bed should be elevated to 35–40° for long-term bedridden patients if there is no contraindication, and the patient should be in appropriate position when feeding the patient; (2) oral hygiene should be maintained to reduce bacterial colonization in the oropharyngeal area; (3) for elderly patients with severe dysphagia who have already experienced aspiration, physicians should evaluate the risks and benefits of nasal feeding *via* indwelling gastric tube; (4) antipsychotic drugs, antihistamines and anticholinergic agents should be avoided or decreased[135,322,323] (II B).

10 | SECTION 8. PROPHYLAXIS

Smoking cessation,[1] avoid excessive alcohol drinking, adequate nutrition and good oral health[324] are all helpful in preventing pneumonia (III B). Good hand hygiene habits should be maintained. During an episode of respiratory tract symptoms such as coughing or sneezing, wearing a mask or using tissues or elbow clothes to cover the nose and mouth can reduce the dissemination of respiratory tract pathogens[325] (III A).

Vaccination against *S. pneumoniae* can reduce the risk of pneumonia in specific populations. The *S. pneumoniae* vaccines currently in use include pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV).

In China, 23-valent pneumococcal polysaccharide vaccine (PPV23) has been on the market. It can effectively prevent invasive *S. pneumoniae* infections.[326] PPV23 is recommended for the following populations (I B): (1) age $\geq$ 65 years; (2) age $<$ 65 years, but with chronic pulmonary disease, chronic cardiovascular disease, diabetes mellitus, chronic renal failure, nephrotic syndrome, chronic hepatic disease (including hepatic cirrhosis), alcoholism, cochlear implant, cerebrospinal fluid leakage, immunodeficiency or functional or organic asplenia; (3) long-term residents in nursing homes or other medical institutions; (4) smokers.[327] For the above patients, one dose of vaccine by intramuscular or subcutaneous injection is recommended. Usually, repeat vaccination is not advised for immunocompetent individuals, although it is appropriate for individuals under 65 years of age, but with chronic renal failure, nephrotic syndrome, functional or organic asplenia or immunodeficiency. There should be at least a 5-year interval between two doses of PPV23. Repeat vaccination is not necessary for the individuals who are at least 65 years of age at the time of first vaccination (I B).

The 13-valent pneumococcal conjugate vaccine (PCV13) can cover 70%-80% of *S. pneumoniae* serotypes in China,[328,329] associated with excellent immunogenicity,[330] but it has not been available in China market. PCV13 vaccination strategy: adults aged $\geq$ 65 years who have not received *S. pneumoniae* vaccination should receive 1 dose of PCV13, and 1 dose of PPV23 within 6–12 months afterward; adults aged $\geq$ 65 years who have received one or more doses of PPV23 should receive 1 dose of PCV13 at least one year after the latest dose of PPV23; adults who have received PPV23 before the age of 65 should receive PCV13 after 65 years old (at least one year after the last vaccination), and can repeat PPV23 vaccination at least 6–12 months later, but there should be at least a 5-year interval between the two doses of PPV23[331] (I B).

Influenza vaccines can prevent influenza or reduce influenza-associated symptoms.[332,333] They also have some protective effects against influenza pneumonia and bacterial pneumonia secondary to influenza.[334] The target population of influenza vaccines is broader than that of *S. pneumoniae* vaccines. See the Chinese Guidelines for Diagnosis and Treatment of Influenza[101] and visit the website for National Influenza Center[335] for details. One dose of influenza vaccine is recommended per annual influenza season[1] (I A). Combination of pneumococcal vaccines with influenza vaccines can decrease mortality in elderly patients[336] (II B).

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